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TABLE OF CONTENTS

Reliability of Some Adrenal Function Tests C. L. COPE, D.M., F.R.C.P., and E. G. BLACK, B.SC. 1117

Blood-group Antibodies and Red-cell Destruction—II P. L. MOLLISON, M.D., F.R.C.P. 1123

Case of Carbon-monoxide Poisoning with Complications R. C. JACKSON, M.R.C.P.Ed., N. V. BUNKER, M.B., W. J. ELDER, M.B., and P. J. O'CONNOR, M.D., M.R.C.P.Ed., D.P.M. 1130

Artificial Respiration and an Artificial Kidney for Severe Barbiturate Poisoning G. E. HONEY, D.M., M.R.C.P., and R. C. JACKSON, M.R.C.P.Ed. 1134

Griseofulvin in Treatment of Infections of Scalp Due to Microsporum Canis MARTIN BEARE, M.D., M.R.C.P., and DONALD MACKENZIE, PH.D., B.SC. 1137

Griseofulvin in Treatment of Persistent Fungal Infections of the Skin A. J. E. BARLOW, M.D., F. W. CHATTAWAY, PH.D., G. K. HARGREAVES, M.B., M.R.C.P.Ed., and C. J. LA TOUCHE, M.SC., L.A.H. 1141

The Muscular Lesion in Hyperthyroidism T. M. D. GIMLETTE, M.D., M.R.C.P. 1143

The Epileptic in Relation to Pregnancy HELEN DIMSDALE, M.D., F.R.C.P. 1147

Preliminary Report on Chlorpromazine in Tetanus AJAI SHANKER, M.D., and L. S. MEHROTRA, M.B. 1150

Anaemia in the Elderly ADRIAN SEMMENCE, M.D., D.Obst.R.C.O.G. 1153

MEDICAL MEMORANDA

Congenital Absence of Gall-bladder Associated with a High Caecum and Absence of Ascending Colon. D. A. REID, M.B., F.R.C.S.Ed. 1154

Primary Varicella Pneumonia. O. MCCARTHY, M.B. 1155

BOOK REVIEWS 1157

DRUG TREATMENT OF DISEASE

Drugs in the Treatment of Seborrhoea. J. T. INGRAM, M.D., F.R.C.P. 1167

GENERAL ARTICLES AND NEWS

Night Calls: Their Frequency and Nature in One General Practice. J. H. F. BROTHERSTON, M.D., D.P.H., F.R.C.P.Ed., and others 1169

College of General Practitioners 1172

Procaine Therapy in Old Age 1175

To-day's Drugs 1176

OBITUARY 1184

MEDICAL NOTES IN PARLIAMENT 1188

VITAL STATISTICS 1192

MEDICAL NEWS 1194

BIRTHS, MARRIAGES, AND DEATHS 1196

QUESTIONS AND COMMENTS 1197

MEDICO-LEGAL

The Defence of "Usual Practice" in Negligence Cases 1190

Speeding on Emergency Calls 1191

LEADING ARTICLES

Testing Adrenocortical Function 1160

Tremor and Stability 1161

"H3" 1163

Registering Medical Auxiliaries 1164

ANNOTATIONS

Griseofulvin 1165

New Industrial Hazards 1165

Hospital Costs 1166

CORRESPONDENCE

Accident Service for the Nation. JOHN FRY, M.D.; H. DENIS WHITE, M.B.; J. FERGUS KING, D.F.C., M.B. 1176

Leukaemia and Radiation. D. W. POLHEMUS, M.D. 1177

Conspicuous Hearing-aids. AMY M. PANTIN, M.B.; J. S. MARTIN, F.R.C.S. ..1177

Recording Speech and Respiration. L. R. C. HAWARD 1178

Auscultation on the Gramophone. E. C. ATKINSON, M.B. 1178

Schultz-Dale Test for Carcinoma. J. G. MAKARI, M.D. 1178

SUPPLEMENT

Full Contents on First Page of Supplement

Speaking Personally. L. A. G[illespie], M.R.C.S., L.R.C.P. 169

Psychological Medicine Group Committee 172

S.H.M.O. Group Council 172

CORRESPONDENCE—*contd.*

Behind the Depressive Syndrome. ROBERT THOMPSON, D.P.M. 1179

Gangrene after Intramuscular Chlorpromazine. W. J. O'CONNELL, M.B. 1180

Osteomalacia in Asian Immigrants. M. N. PAI, M.R.C.P. 1180

Personal Medical Records. J. EDIS, M.R.C.O.G. 1180

Temporary Paralysis after Polio Vaccine. N. H. BARLEY, M.B. 1181

Carcinoma of Fallopian Tube. C. S. LYGONIS, M.D. 1181

Tongue-tie. MICHAEL C. OLDFIELD, D.M., M.Ch. 1181

New Sulphonamides. F. T. THORPE, D.P.M. 1182

When to Tie the Cord. R. A. R. WALLACE, F.R.C.S. 1182

Syphilis and Mental Deficiency. GLADYS M. SANDES, F.R.C.S. 1182

"No Connexion Whatsoever"? H. B. WRIGHT, M.B., F.R.C.S. 1183

Service Psychiatrists. S. LASK, M.D. ..1183

Phenoxymethylpenicillin and Drowsiness. W. M. C. HALLINAN, M.R.C.S. 1183

Common Medicines Abroad. A. T. [illegible], F.R.C.S. 1183

Oxytocic Principles and Antagonists in Obstetrics. OSWALD LLOYD, F.R.C.O.G., [illegible] BROWN, F.R.C.S. 1184

[illegible] in the Market Place. E. N. CALLUM, F.R.C.S.Ed. 1184

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The Atrial Sound and the Atrial Component of the First Heart Sound. *Priscilla Kincaid-Smith and John Barlow*

The Atrial Sound in Hypertension and Ischaemic Heart Disease. *Priscilla Kincaid-Smith and John Barlow*

Properties and Biological Behaviour of Coomassie Blue. *S. H. Taylor and J. M. Thorp*

Clinical Applications of Coomassie Blue. *S. H. Taylor and J. P. Shillingford*

A Twin Oscilloscopic Vectorcardiograph. *A. J. V. Cameron, T. D. V. Lawrie, and J. H. Wright*

Unexplained Heart Failure in the Aged. *G. A. Ross and R. R. Wilson*

Rupture of Aortic Aneurysms into the Gut. *G. A. Gresham and H. R. M. Johnson*

The Cardiogram of Congenital and Acquired Right Ventricular Hypertrophy. *J. F. Goodwin and Z. H. Abdin*

The Pathogenesis of Infarction of the Right Ventricle. *W. G. Wade*

Congenital Kinking of the Aortic Arch. *J. N. Pattinson and R. G. Grainger*

Perforation of the Interventricular Septum in Myocardial Infarction. *J. M. Swithinbank*

Case Reports:

Endocardial Fibro-elastosis in a Young Adult. *R. Mulcahy and R. P. Towers*

Dissecting Aneurysm of Aorta Associated with Goldblatt Kidney. *G. D. Owen and P. N. Coleman*

John Hay. *Maurice Campbell and E. Wyn Jones*

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Index

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 28 1959

THE RELIABILITY OF SOME ADRENAL FUNCTION TESTS

BY

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AND

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Ever since the hormone-producing role of the adrenal cortex became clearly recognized attempts have been made to obtain, by chemical means, measures of its varying activity under different conditions and in different diseases. The chemical tests developed have in the main attempted to estimate the quantity of adrenocortical metabolites appearing in the urine, though more recently it has become possible to measure directly the concentration of adrenal hormone in the plasma. It has not been possible to measure the total mass of adrenal metabolites in urine because the nature of more than half of these has been, and indeed still is, quite unknown. The only course, therefore, has been to estimate certain types of compounds which represent one group of the metabolites and to deduce the behaviour of the adrenal cortex from the results of such estimates.

Two difficulties were encountered in this approach. First, the complex composition of urine rendered difficult the separation of the chosen group of adrenal metabolites from a wide variety of contaminating substances. Secondly, the extent to which the chemical estimates varied with the true activity of the adrenal cortex was completely unknown, though indirect deductions could sometimes be drawn. Because of these fundamental difficulties the only satisfactory or possible way in which the validity of a test could be assessed was by comparing the chemical results obtained with the results of careful clinical impression. To use such an arbiter of the validity of a test is fraught with danger, for the clinical diagnosis is often limited in accuracy and the essential purpose of the test is to improve this accuracy. The chemical assay gives a quantitative measure, and this the clinical assessment is rarely able to do. Because of lack of other criteria of validity it became usual to regard any test as justified if it gave low figures in Addison's disease and figures well above the normal range in conditions of hyperadrenalism such as Cushing's syndrome or after corticotrophin stimulation. By such relatively crude criteria were most of the earlier tests of adrenal actively justified.

With the great progress which has taken place during the past 10 years in the chemistry and nature of these adrenal hormones and their metabolites, and in their methods of estimation, such crude criteria of validity are no longer sufficient, and a more critical appraisal may justifiably be expected.

Much additional information about these tests can be obtained by deliberately altering the intensity of the adrenal cortical activity and noting the extent to which the various measures follow the changes induced. Thus stimulation of the gland is readily and rapidly achieved with corticotrophin, and inhibition of the gland is effected with equal facility by the administration of suitable synthetic steroids of the types introduced for modern adrenal steroid therapy.

The ordinary techniques of adrenal analysis now usually employed are the urinary 17-ketosteroids and the more recently introduced 17-ketogenic steroids of Norymberski, Stubbs, and West (1953). But other methods are also available, though their clinical use has so far been very inadequately explored. Since one of the major products of the adrenal cortex is cortisol it is logical to attempt to estimate this in plasma or in urine.

The usefulness of estimations of the plasma cortisol has been well explored (Bayliss, 1955), but the results are handicapped by the fact that quite wide natural fluctuations occur and there is a considerable diurnal rhythm. The results are of clinical value in detecting hyperadrenalism, either natural as in Cushing's disease or induced as after corticotrophin stimulation, but they are not so satisfactory for detecting hypoadrenal states because even in normal subjects the plasma cortisol may sink to a low level comparable to that found in Addison's disease.

In contrast to the work done on plasma cortisol levels, very little investigation has been made on the clinical value of urinary cortisol assays. The amount of cortisol appearing in urine is small; it is of the same order as the concentration in blood. But since much larger samples of urine are available, the estimation of urinary cortisol with an accuracy sufficient for clinical purposes is not a difficult procedure. A method for this purpose has been described by Cope and Hurlock (1954) which has an accuracy of about $\pm 20\%$, though Vermeulen (1957) has found he can achieve an accuracy of $\pm 15\%$ with the method.

The estimation of urinary cortisol can, of course, scarcely be justified unless the clinical value to be gained is commensurate with the analytical effort involved.

Another measure which also offers theoretical possibilities is the determination of the amount in the urine of the main cortisol metabolites—tetrahydrocortisone and tetrahydrocortisol. The estimation of these is now a feasible clinical proposition, though the analysis is rather more difficult and takes longer than does the urinary cortisol because a preliminary enzyme

hydrolysis is needed. Because they call for greater technical skill than is ordinarily required for the more routine chemical pathology determinations such analyses could be justified only if they provided information not readily to be obtained by more simple means.

We have explored the relative value of these and some other tests under a variety of clinical circumstances in an effort to determine whether they offer advantages to the clinician.

Adrenal Tests in Hyperadrenalism

One of the best ways to compare the relative clinical value of such tests is to observe the extent to which various measures diverge from the mean normal figure under abnormal clinical conditions.

This has been done in a consecutive series of 12 cases of clinically established Cushing's syndrome. In Fig. 1 are shown the mean results obtained in this series. The biggest divergence from the normal mean is seen to occur with the urinary cortisol, which rises to an average of eight times the normal value, a rise which may be compared with that for the 17-ketogenic steroids, which is on average four times the normal mean. The figures for 17-ketosteroids express the well-known fact that this group of steroids is not significantly raised in Cushing's syndrome, a fact which shows that little relation is to be expected between actual cortisol production and the 17-ketosteroid output. A mean increase for 17-ketosteroids to only 1.4 times the normal mean can scarcely be regarded as a significant rise. It is of interest, too, that the increase in the excretion of the major metabolites, tetrahydrocortisone and tetrahydrocortisol, is also relatively small, suggesting that these indices of adrenocortical activity are comparatively insensitive ones for recording increased adrenal activity.

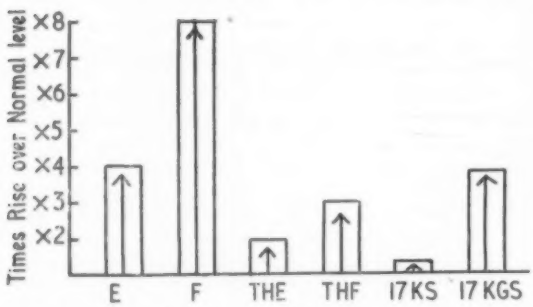

FIG. 1.—Changes in urinary excretion of various steroids in Cushing's syndrome. E=Cortisone. F=Cortisol. THE=Tetrahydrocortisone. THF=Tetrahydrocortisol. 17KS=17-Ketosteroids. 17KGS=17-Ketogenic steroids. Mean of 12 cases.

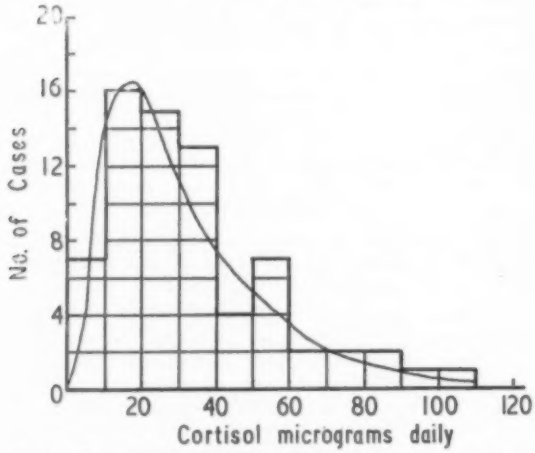

FIG. 2.—Range of urinary cortisol excretion (70 convalescent non-endocrine cases).

Figures such as these are, however, significant only when considered in relation to the normal scatter.

The normal scatter for urinary cortisol concentration is shown in Fig. 2. This distribution is not appreciably affected by ordinary non-endocrine medical disorders. It will be noted that the range is from a small trace up to about 100 μg. a day. The mean for the group is 43 μg. daily. From this curve it is clear that low concentrations of urinary cortisol do not necessarily indicate hypoadrenalism and that therefore the urinary cortisol cannot usefully be employed to detect hypoadrenalism. An excretion of detectable amounts, 40 μg. or more, of cortisol is irrefutable evidence that cortisol production is taking place in that individual provided there is no exogenous source.

We have seen that the mean urinary cortisol in Cushing's syndrome is eight times the normal mean or about 320 μg. daily. In Fig. 3 the range of values encountered in this series of clinically diagnosed cases is shown to have only a small overlap with the normal range. In contrast to this are shown the ranges for ketogenic steroids in normals and the ranges found in small series of cases of Cushing's syndrome derived from three papers taken from the literature. It will be seen that the overlap between normal and abnormal is very much greater in the case of the 17-ketogenic steroids than it is with the urinary cortisol excretion.

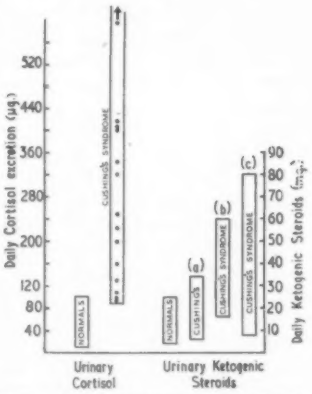

FIG. 3.—Comparison of urinary cortisol and urinary ketogenic steroids in Cushing's syndrome. (*a*) Levell, Mitchell, Paine, and Jordan (1957). (*b*) Moxham and Nabarro (1956). (*c*) Breuer and Nocke (1957).

Essentially similar results are obtained when these tests are compared in the adrenal hyperactivity produced by corticotrophin.

Thus it may be said that estimation of the urinary cortisol is at least twice as sensitive in detecting the hyperadrenalism of Cushing's syndrome as is the 17-ketogenic steroid assay, which is its nearest competitor.

Why this should be so cannot as yet be explained with certainty. But there seems a strong probability that it can be related to the peculiar protein binding that cortisol undergoes in plasma. When plasma cortisol levels are in the normal or low normal range, 90 to 95% of the total is loosely bound to protein. At a concentration of 10 μg. per 100 ml., therefore, only 0.5 to 1 μg. will be free (Daughaday, 1958). If a five-times

rise in plasma cortisol concentration occurs as a result of enhanced adrenocortical activity, then only 75% is bound, so that 12.5 mg. will remain unbound and easily filterable. Thus a five-times rise in concentration can apparently lead readily to a 12 to 25 times rise in filterable cortisol.

Adrenal Tests During Adrenal Inhibition

When adrenal steroids are administered to the human subject suppression of adrenocortical activity rapidly ensues and cortisol production falls rapidly to minimal levels.

If the original adrenal activity before the steroid dose was great enough to lead to an adequate urinary cortisol output, then this inhibition can readily be measured or detected by following the urinary cortisol concentrations daily. This is, of course, only possible if the administered steroid is not either cortisone or cortisol, for both these will be absorbed into the blood-stream as cortisol and will in part appear as such in the urine. Their appearance will naturally mask the changes which are occurring in endogenous cortisol production. But if the administered steroid is one of the modern synthetic ones—prednisone, 9α-fluorocortisol, triamcinolone, etc. the appearance of these in the urine will not interfere appreciably with the estimation of urinary cortisol and the resultant adrenal suppression can therefore be easily followed by measuring the urinary cortisol daily.

It is instructive to measure such an adrenal suppression with the various adrenal tests under consideration. The mean changes which occurred in a group of six cases of Cushing's syndrome are shown in Fig. 4. From this it is apparent that urinary cortisol drops more promptly and more completely than any of the other measures. The tetrahydro metabolites drop rather more slowly, but it will be seen that both 17-ketosteroids and 17 ketogenic steroids fall much more sluggishly and that during the six days of observation neither was reduced by more than 50% of its starting value. It is clear, therefore, that urinary cortisol is very much more sensitive than other indices in general use for detection of adrenal inhibition. This fact has some clinical importance, for the possible value of adrenal-inhibition tests has recently been explored as an indicator of corticotrophin-dependent hyperactivity. It is scarcely justifiable to assess the value of such a test by using methods of analysis which are insensitive. That a mild adrenal inhibition may be missed completely by the use of such

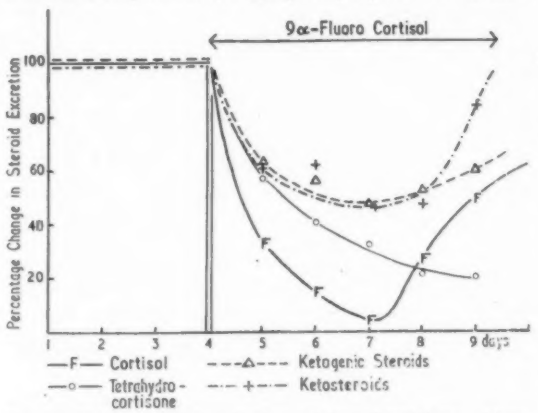

FIG. 4.—Urinary steroids as indices of adrenal inhibition. Mean of six cases.

methods was shown by Cope and Harrison (1955), who reported a case in which adrenal inhibition was revealed by urinary cortisol fall, but in which no change was observed in the urinary 17-ketogenic steroids.

This high sensitivity of the urinary cortisol as an index of reduction of adrenal activity probably has its explanation also in protein-binding, for as a result of this binding the amount of free diffusible cortisol in plasma will fall much more rapidly than does the total plasma cortisol concentration.

Why the 17-ketogenic steroids should drop so slowly and imperfectly when the adrenal cortex is inhibited by steroid therapy is not entirely clear. A major factor is likely to be the need to eliminate all these metabolites by renal excretion in contrast to the cortisol, which has a very short half-life in the blood-stream and disappears rapidly by decomposition. Another factor no doubt will be the fact that if the administered inhibiting steroid appears in the urine it may be estimated as 17-ketogenic steroid, thus in part disguising the true fall.

Function Tests in Adrenal Hypofunction

From the distribution curve of normal, or non-endocrine, urinary cortisol values (Fig. 2) it is apparent that a concentration near the lower limit of detection of the method—that is, below 15 μg. a day—may be encountered in normal subjects. It follows, therefore, that a low urinary cortisol output is not evidence of the presence of a pathological degree of hypoadrenalism. But for obtaining such evidence the urinary output of tetrahydrocortisone, or of tetrahydrocortisol, or of the two combined, is a much more valuable measure. In this respect its value stands in sharp contrast to its failure to indicate well an increasing adrenal activity.

The situation may perhaps best be explained by an analogy. The intensity of burning of a fire is generally best measured by the heat produced, but to determine whether the fire has been extinguished it is often preferable to observe whether or not smoke is still being produced. In the adrenal the smoke is represented by the metabolites, the tetrahydro compounds.

The distribution curve for tetrahydrocortisone or tetrahydrocortisol excretion under ordinary circumstances is a broad one. For the former steroid it ranges from about 1,000 μg. daily to 4,000 μg., and occasionally more.

The great advantage of this measurement over other measures, such as the 17-ketosteroids or the 17 ketogenic steroids, is that the determination of tetrahydrocortisone is a specific one which is not subject to appreciable interference by non-specific chromogens or, as a rule, by other interfering steroids. As a result the estimation can be carried out with an accuracy quite sufficient for clinical purposes even when the tetrahydrocortisone excretion is reduced to one-tenth or less of the minimum value for the normal range. Such sensitivity is scarcely feasible with either 17-ketogenic steroid or 17-ketosteroid assays.

The lowest degrees of adrenal cortisol production are found in hypopituitarism rather than in Addison's disease. For in the latter the factor commonly determining the onset of symptoms is the aldosterone deficiency rather than the cortisol shortage, and the former may be serious before the latter has reached extreme degrees. In both conditions the tetrahydrocortisone excretion is much reduced, often below 250

μg. a day. The mean figures we have observed for a group of 12 cases of hypoadrenalism due to these causes was for hypopituitarism (six cases) 200 μg. and for Addison's disease (six cases) 390 μg. In severe cases of either condition the tetrahydrocortisone output may fall to less than 5% of the normal mean.

But a diminished output of tetrahydrocortisone may be due to impaired hepatic function, with resultant impaired metabolism of a normal quantity of cortisol formed. This is especially likely to occur in advanced hepatic cirrhosis.

Though clinical confusion between hepatic cirrhosis and hypoadrenalism is likely to be a rare problem, it could arise, for instance, in some cases of haemochromatosis. The severer forms of each can, however, usually be distinguished without great difficulty by means of the tetrahydrocortisone assay.

In a group of seven cases of advanced hepatic cirrhosis with severe impairment of liver function, the range of tetrahydrocortisone excretion was found to be from 220 μg. to 1,300 μg. daily, with a mean of 670 μg. The distribution of these cases is shown in Fig. 5, and from this it is apparent that any clinical

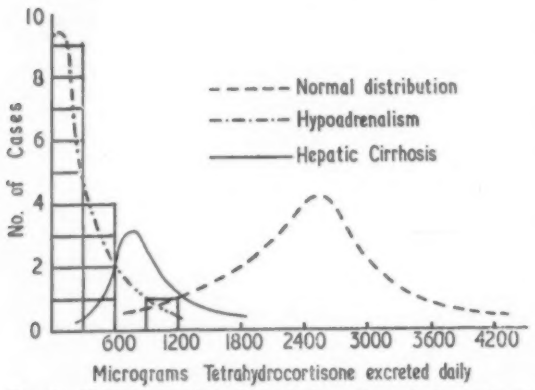

FIG. 5.—Urinary excretion of tetrahydrocortisone in hypoadrenal states and in hepatic cirrhosis.

confusion between hypoadrenalism and severe hepatic cirrhosis could usually be resolved satisfactorily by means of this test.

Illustrative Difficult Cases

But though tetrahydrocortisone excretion provides a valuable method of recognizing hypoadrenalism, useful information may sometimes be obtained in difficult clinical circumstances by the demonstration of cortisol in the urine. While no certain conclusions about adrenal function can be drawn from the finding of only a trace of cortisol in the urine, yet the demonstration of an adequate or generous normal quantity of cortisol in the urine is positive proof that cortisol is being produced in the body in appreciable quantity. This seems to exclude hypopituitarism of any severity, and excludes also severe degrees of Addison's disease, but it does not exclude Addison's disease of moderate degree, in which aldosterone formation may be damaged much more than cortisol production. The recognition of urinary cortisol may be particularly valuable in the difficult clinical case, and has the great advantage that the reducing steroid spot on the toluene/propylene glycol chromatogram at the appropriate point is not subject to contamination or confusion by interfering substances and may be accepted as cortisol with reasonable certainty. In a large series of chromatographic analyses of urine extracts obtained from a wide variety of clinical subjects we have never recognized a reducing contaminant at the cortisol spot. This is not true in our experience of most other reducing steroid spots on the chromatograms of urine extracts.

Two cases may be quoted which illustrate well the value of urinary cortisol estimations.

Case 1.—The patient was a large muscular healthy-looking man aged 45. He had been diagnosed as suffering from Addison's disease in 1938. He joined a Guards Regiment in the last war and served satisfactorily until he was recognized by a medical officer who had treated him for Addison's disease in civil life five years previously. After resultant discharge from the Army he took to playing water-polo for a crack team. He was seen in 1955 because of reduction of exercise tolerance below his previously exceptionally good performance. He had a fine muscular physique, no pigmentation, and normal blood-pressure. Serum sodium and chloride were normal. Water-excretion test gave 94% output in 4 hours. The 17-ketosteroids were 6 mg. Both adrenals were very intensely calcified and 5 cm. in diameter. An intravenous corticotrophin-stimulation test caused no change in function as judged by 17-ketosteroid excretion or urinary or plasma cortisol (4 μg. per 100 ml.).

The diagnostic ambiguity in this patient was in large measure resolved by the demonstration of 20 μg. a day of cortisol in the urine together with 1,600 μg. of tetrahydrocortisone and 380 μg. of tetrahydrocortisol. This provided proof that he was indeed producing good supplies of cortisol. It was later possible to show, by the use of ^{14}C-cortisol, that his daily cortisol production was 19 mg. daily, an amount adequate for most purposes.

Case 2.—A man aged 53 of gipsy origin, was known to be suffering from a carcinoma of the bronchus. He was heavily pigmented, especially in the flexures. There was extensive buccal pigmentation. His blood-pressure was 100/55. 17-Ketosteroid excretion was 1 mg. daily. A water-excretion test gave an output in four hours of only 25% of the dose. After 50 mg. of cortisone acetate this was increased to 41% and after 100 mg. diuresis rose to 93% of the dose. The serum sodium was 122 mEq and chloride 96 mEq. An intravenous corticotrophin-stimulation test produced an ambiguous result. The suspicion was strong that Addison's disease had arisen as a complication due probably to metastatic invasion of the adrenal glands. Chromatography of a simple *p*H 1 extract ($CHCl_3$) of the urine revealed a high normal (103 μg.) output of cortisol, and this practically excluded even mild hypoadrenalism. At subsequent necropsy the adrenal glands showed no metastatic or other involvement and the cortices were mildly hypertrophied.

A similar clinical problem arises not infrequently in advanced tuberculosis not responding to modern antituberculous therapy. In such persons the combination of pigmentation, low blood-pressure, asthenia, low serum sodium, and low serum chloride inevitably raises the question of a complicating Addison's disease due to adrenal involvement by the tuberculous process. The finding of a low 17-ketosteroid output, which is usual in wasting disorders, will enhance the suspicion.

Yet such subjects usually excrete high normal amounts (>60 μg.) of cortisol in the urine, and the demonstration of more than 500 μg. of tetrahydro-

cortisone daily in the urine will afford additional proof that cortisol production is continuing.

Relation of Adrenal Tests to Cortisol Production Rate

It is thus apparent that these various measures of adrenal activity differ greatly in their suitability for use under differing clinical conditions. It is now possible to obtain a useful estimate of the actual daily cortisol production from the human adrenal cortex by making use of radioactive cortisol labelled with ^{14}C. With this it becomes feasible to compare these various tests with the actual daily cortisol production and to determine the extent to which they actually reflect the true production rates of cortisol (Cope and Black, 1958).

In Fig. 6 is plotted the daily cortisol production rate against the daily elimination of cortisol in the urine. It will be seen that the amount appearing in the urine

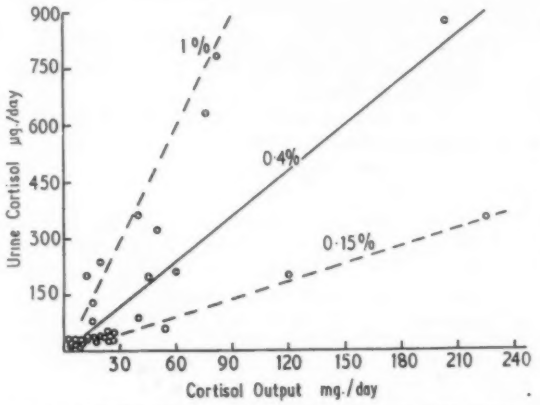

FIG. 6.—Comparison of cortisol production rate with urinary cortisol excretion.

represents from 0.15 to 2% of the actual daily production. The extent of the scatter is such that quantitative conclusions about the absolute rate of cortisol production cannot be drawn from knowledge of the urinary cortisol. Thus a urinary cortisol excretion of 75 μg. may be associated with a cortisol production of 15 to 50 mg. daily, and one of 340 μg. with production rates of from 40 to 225 mg. a day. This lack of correlation is likely to be due far more to individual variations in the percentage of cortisol bound to protein than to any variations in renal function.

A rather better agreement with the production rate of cortisol is seen in the urinary excretion of tetrahydrocortisone or of tetrahydrocortisol. At low and normal levels of activity about 20% of the total cortisol produced appears in the urine in the form of these metabolites. But as the activity of the adrenal increases and cortisol production is raised, the percentage of the total appearing in the urine in the form of the tetrahydrocortisone or tetrahydrocortisol tends to fall until at high productions it may be as low as 5%. To some extent this fall may explain the relative insensitivity of urinary tetrahydrocortisone as an index of raised adrenocortical activity.

The relationship between urinary 17-ketosteroid output measured by the classical routine method and the cortisol production rate is shown in Fig. 7. The lack of any useful correlation is in conformity with clinical impressions and with the well-recognized fact that 17-ketosteroid output is not necessarily raised in Cushing's syndrome. From Fig. 7 it will be seen that a 17-ketosteroid output of 25 mg. may occur with a cortisol production of 10 mg. daily and that an output of 30 mg. occurred in a patient with cortisol production of 225 mg. a day. It is clear that no useful conclusions about the actual daily cortisol production can be drawn from the 17-ketosteroid excretion.

With the 17-ketogenic steroids of Norymberski *et al.* (1953) the relationship is a good deal more encouraging (Fig. 8). It is evident that, though considerable scatter occurs, the points lie about a line which represents an excretion of 50% of the total cortisol production in the form of analysable 17-ketogenic steroids. But the degree of scatter is not appreciably reduced at the lower levels of cortisol production. The normal range of cortisol production is up to about 25 mg. daily, and none of the patients with florid Cushing's syndrome whom we have so far examined have had cortisol production

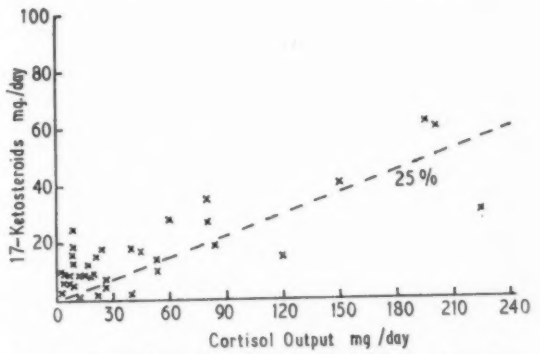

FIG. 7.—Comparison of cortisol production rate with urinary 17-ketosteroid excretion. (Broken line represents 25% of cortisol produced, not the line of best fit.)

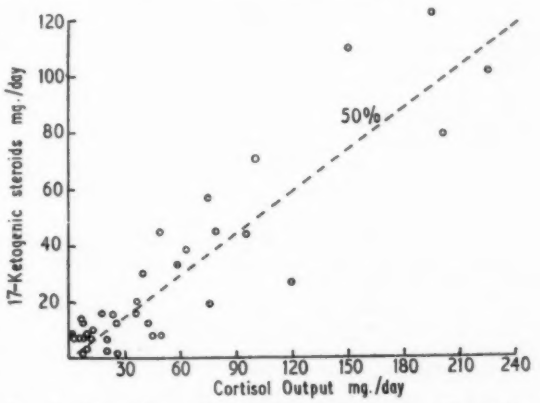

FIG. 8.—Comparison of cortisol production rate with urinary 17-ketogenic steroid excretion. (Broken line represents 50% of cortisol produced.)

rates above 90 mg. daily. In this range, where laboratory guidance for the clinical problem is most needed, it will be seen that there is a relatively poor relation between cortisol production and observed urinary ketogenic steroid excretion. To some extent no doubt this scatter is attributable to experimental errors in carrying out the 17-ketogenic steroid

estimations, for by its nature the 17-ketogenic steroid method is subject to increasing percentage errors at its lower range of values, whereas the isotope method of measuring the cortisol production rate is not subject to such limitations at low outputs.

All our ketogenic steroid estimations were carried out in duplicate, and in many of the instances where an unexpected result was obtained a check was made with the results of an independent routine laboratory analysis. There is little doubt, therefore, that much of the scatter is a real discrepancy between the ketogenic steroid output and the estimated cortisol production. In a few instances the apparent excretion of 17-ketogenic steroids actually exceeds the estimate of the cortisol produced. But all these occur at cortisol production rates below 10 mg. daily and with ketogenic steroids below 15 mg. a day. It is likely in these either that interfering substances have inflated the true 17-ketogenic steroid figure or that small amounts of ketogenic steroids are derived from sources other than cortisol metabolism. But from the relatively small number of comparisons made here and plotted in Fig. 8 the following general conclusions may be made. (1) A 17-ketogenic steroid output in excess of 25 mg. indicates a cortisol output raised well above the normal upper limit and generally in excess of 35 mg. daily. (2) The higher the 17-ketogenic steroid output the more this tends to approach 50% of the actual cortisol production. (3) With 17-ketogenic steroid outputs in the normal or low range—that is, below about 20 mg. a day—the relation to actual cortisol production rate is so indefinite, and the scatter is so wide, that no conclusions about the cortisol production rate can be drawn save that it is probably not greatly raised above normal. But it may be observed that in one instance a cortisol production of 75 mg. daily was associated with a 17-ketogenic steroid output in the urine of only 20 mg.

General Conclusions

It is thus apparent that the 17-ketogenic steroid determination has its limitations in precisely the range of borderline degrees of hyperfunction of the adrenal where its help is most needed. But of all the tests which have been considered here the urinary 17-ketogenic steroid output correlates better than any other with the actual cortisol production as estimated by the isotope technique. Maybe with the borohydride method results will be still better (Appleby, Gibson, Norymberski, and Stubbs, 1955).

The other tests, too, have their shortcomings. The urinary cortisol, most sensitive in the detection of increased adrenal activity or of inhibition of hyperactivity, is quite unsatisfactory for the detection of hypofunction. The urinary 17-ketosteroid output bears no relation to actual cortisol production, and the tetrahydrocortisone excretion, very valuable for providing evidence of gross hypoadrenalism, is not a good index of increased adrenal activity.

It follows, therefore, that ideally the test used should be adapted to the problem at hand. For routine clinical purposes the 17-ketogenic steroid estimation is probably the best general test, but its limitations should be recognized. For research purposes it may not be sensitive enough to detect the changes which are being sought, and more specific steroid analyses may then be necessary. The use of radioactive cortisol offers the best ultimate prospects of solving this problem, but at present its great expense and the shortage of supplies preclude its use except for special research purposes; but in the absence of this the relatively simple urinary cortisol assay can often produce evidence of great clinical value in the ambiguous case.

Summary

Adrenal-function tests vary widely in their sensitivity to different conditions, and therefore in their suitability for various purposes.

Urinary cortisol excretion is more than twice as sensitive as ketogenic steroid excretion for demonstration of adrenal hyperactivity and for detecting inhibition of such hyperactivity.

Urinary cortisol excretion is unsuitable for detecting adrenal hypofunction, but this is sensitively revealed by measuring the main cortisol metabolites—tetrahydrocortisol and tetrahydrocortisone — in the urine. Excretions as low as 5% of normal can still be measured with sufficient accuracy..

The excretion of various steroids and steroid groups has been compared with the daily cortisol production rate measured by isotopic means.

There is no relation between 17-ketosteroid excretion and the daily cortisol production.

There is a poor correlation between daily cortisol production and urinary cortisol excretion.

At high rates of adrenal activity the urinary excretion of 17-ketogenic steroids is approximately half the daily cortisol production.

In low, normal, or moderately raised adrenal activity the correlation between cortisol production rate and 17-ketogenic steroid excretion is poor, and no conclusion is justified about the former from the magnitude of the latter.

Adrenal function tests need to be carefully selected for their suitability for the purpose intended.

Our thanks are due to the Medical Research Council for a grant to one of us (E.G.B.), and to the United States National Institute of Health, Division of Research Grants, for a generous gift of ^{14}C-labelled cortisol. We are grateful to Miss Sylvia Hughes for valued technical assistance.

References

Appleby, J. I., Gibson, G., Norymberski, J. K., and Stubbs, R. D. (1955). *Biochem. J.*, **60**, 453.
Bayliss, R. I. S. (1955). *Brit. med. J.*, **1**, 495.
Breuer, H., and Nocke, W. (1957). *Klin. Wschr.*, **35**, 187.
Cope, C. L., and Black, E. G. (1958). *Clin. Sci.*, **17**, 147.
—— and Harrison, R. J. (1955). *Brit. med. J.*, **2**, 457.
—— and Hurlock, B. (1954). *Clin. Sci.*, **13**, 69.
Daughaday, W. H. (1958). *J. clin. Invest.*, **37**, 511.
Levell, M. J., Mitchell, F. L., Paine, C. G., and Jordan, A. (1957). *J. clin. Path.*, **10**, 72.
Moxham, A., and Nabarro, J. D. N. (1956). Ibid., **9**, 351.
Norymberski, J. K., Stubbs, R. D., and West, H. F. (1953). *Lancet*, **1**, 1276.
Vermeulen, A. (1957). *Acta endocr. (Kbh.)*, **26**, 399.

In a foreword to the Annual Report of the Royal National Institute for the Blind for the year ended March 31, 1959, Mr. GODFREY ROBINSON, Chairman of the Institute's Executive Committee, draws attention to the fact that the R.N.I.B. has, in one year, spent over £1m. on services to the blind, produced nearly 600,000 Braille volumes, periodicals, and leaflets, and succeeded in placing in industry and commerce nearly one trained blind man or woman for each working day. The report says that about 12,000 new names a year are added to the register of blind persons in this country.

BLOOD-GROUP ANTIBODIES AND RED-CELL DESTRUCTION*

BY

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In devising compatibility tests to precede transfusion, and in interpreting them, we need to know the precise relationships between the interactions of red cells and serum *in vitro* and the survival or destruction of the same red cells *in vivo*. An inquiry into this problem can be divided into the following questions:

1. Does any interaction between red cells and serum at 37° C. *in vitro*, however trivial, imply some interference with survival *in vivo*? If so, is the same true for 30° C. *in vitro*, and if not, what is the highest temperature of interaction *in vitro* associated with no effect *in vivo*?

2. Are the characteristics of blood-group antibodies *in vitro* exactly related to their effects *in vivo*? For example, if an antibody binds complement *in vitro* does it bring about the removal of red cells in a different way from that of an antibody which does not bind complement?

3. Is there a close relationship between the potency of an antibody, judged by tests *in vitro*, and the speed and extent of the red-cell destruction which it causes *in vivo*?

4. Do antibodies display precisely the same specificity *in vitro* and *in vivo*? This problem arises particularly in the selection of blood for transfusion to patients with acquired haemolytic anaemia.

5. Is it possible for red cells to be compatible with the recipient's serum *in vitro* and yet to be treated as incompatible after transfusion?

An attempt will be made to answer these questions in turn.

Antibodies Weakly Active in Vitro at 37° C.

It seems to be the rule that any degree of agglutination of a donor's red cells by the recipient's serum at 37° C. *in vitro*, due to a blood-group antibody, implies that there will be at least partial destruction of the red cells if they are transfused. For example, in a subject whose serum contained anti-Mi^a with a titre of 2 at 37° C. almost 100% of Mi(a+) cells were removed with a half-time of 20 minutes (Case 13 of Cutbush and Mollison, 1958). In another case, in which the recipient's serum contained anti-Lu^b giving only very weak agglutination of Lu^aLu^b cells at 37° C. (titre 1 in 1), about 20% of the cells were removed from the circulation with a half-time of about 20 minutes, the rest being removed only over a period of many weeks (Case 12 of Cutbush and Mollison, 1958).

Chaplin (1959) has reported that in some cases of hypogammaglobulinaemia in which the patient's serum agglutinated A or B cells only when undiluted, and then only weakly, A or B cells were sometimes removed with a half-time of a few minutes.

Antibodies which, at 37° C., agglutinate very weakly or not at all, but sensitize red cells to an antiglobulin serum, usually bring about red-cell destruction, even when their titre is very low. There seems to be a large difference between antibodies which bind complement and antibodies which do not. Thus, incomplete antibodies which do not bind complement, such as anti-c or anti-E, when they are very weak (indirect antiglobulin titre about 1 in 4) bring about only very slow red-cell destruction, with a half-time of the order of four or five days (Case 8 of Mollison and Cutbush, 1955; Case 15 of Cutbush and Mollison, 1958). On the other hand, incomplete antibodies which bind complement and have a titre at 37° C. of only 1 in 4 may bring about removal of a proportion of injected red cells with a half-time of a few minutes. One such case, due to anti-Le^b, has been described elsewhere (Mollison, 1959b); Fig. 10 shows another case, in which anti-O was concerned. Since red-cell destruction due to anti-O has probably not been described before, a few details are given.

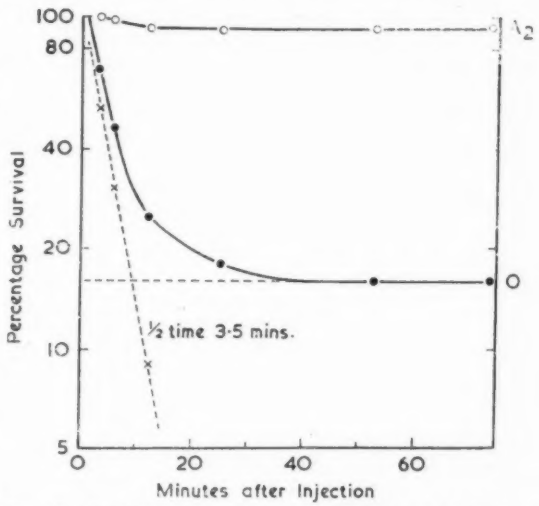

FIG. 10.—Survival of group O and subgroup A_2 red cells in a subject (subgroup A_1) whose serum contained anti-O. *In vitro*, at 25° C., the serum agglutinated O cells and A_2 cells; at 37° C. the reaction with O cells was so weak as to be doubtful and A_2 cells were not agglutinated. At 37° C. the serum, provided that complement was present, sensitized O cells but not A_2 cells to an antiglobulin serum. Most of the group O red cells were rapidly removed from the circulation, and this component is plotted separately as a broken line. The A_2 cells underwent no significant destruction during the hour following injection.

The patient herself belonged to subgroup A_1. Although her saliva inhibited anti-H (extract of *Ulex europaeus*), her red cells were scarcely agglutinated at all by the same extract; normal A_1 cells were agglutinated by the extract. At 25° C. the patient's serum agglutinated group O and A_2 cells but not A_1 cells. The reactions were not inhibited by H substance (secretor saliva). At 34° C. the serum very weakly agglutinated O cells; at 37° C. the reactions were so weak as to be doubtful; the reactions were not enhanced by suspending the cells in serum or albumin; A_2 cells were not agglutinated. At 37° C. the serum sensitized O cells to an antiglobulin serum, but only when the red cells were incubated with complement as well as with antibody. The reaction with A_2 cells was barely detectable.

As Fig. 10 shows, when a small sample of group O cells was injected, 80% of the cells were removed with a half-time of 3.5 minutes; there was no significant destruction of A_2-cells during the 60 minutes for which their survival was followed.

Antibodies Active in Vitro only at Temperatures below 37° C.

It will be generally agreed that an antibody which is inactive above 25° C. *in vitro* is without effect *in vivo*; some examples of tests in such cases have been published

*The second of two Oliver-Sharpey Lectures given at the Royal College of Physicians of London on March 10 and 12, 1959. The first lecture appeared in last week's issue.

(Mollison and Cutbush, 1955; Cutbush and Mollison, 1958). What is difficult is to find cases in which the antibody is inactive at 37° C. *in vitro* but is active at some slightly lower temperature, such as 33° C., so as to discover as precisely as possible the relationship between thermal range of activity *in vitro* and activity *in vivo*. However, one such subject was studied by Cutbush and Mollison (1958). This patient's serum contained an anti-M which agglutinated *MM* cells at 34° C. but not at 37° C., and agglutinated *MN* cells at 31° C. but not at 34° C. At 37° C. no reaction of any kind could be detected between *MM* cells and the patient's serum, either in albumin or using the indirect antiglobulin test. When *MM* cells were injected, about 60% of the cells were removed with a half-time of a few minutes; when *MN* cells were injected there was no destruction whatever during the following hour, but the red cells were removed at a definitely accelerated rate (half-time of several days).

This case suggests the following conclusions: first, a cold antibody whose thermal range *in vitro* extends almost but not actually to 37° C. may bring about very rapid destruction of red cells *in vivo*. This evidently implies that, in cross-matching, an agglutination test performed strictly at 37° C. may not be so reliable as a test performed at a slightly lower temperature. Second, a cold antibody whose thermal range *in vitro* extends to 31° C. or thereabouts but not higher is probably incapable of bringing about rapid destruction of red cells—that is, with a half-time measured in minutes—but may be capable of bringing about the slow destruction of transfused red cells. This latter conclusion agrees well with the observation that in acquired haemolytic anaemia of the cold antibody type the thermal range of the antibody *in vitro* may extend only to 30° C. or 31° C. (Dacie, 1957).

Relationship between Characteristics of Antibodies in Vitro and their Effects in Vivo

On the basis of their reactions *in vitro* antibodies may be divided into the following classes: (*a*) agglutinating and readily haemolytic *in vitro*; (*b*) agglutinating (but not haemolytic); (*c*) incomplete, binding complement; and (*d*) incomplete, not binding complement. The effects which these antibodies produce *in vivo* may be summarized thus:

(*a*) Antibodies which are readily haemolytic *in vitro* bring about intravascular lysis of the majority of injected red cells. Examples have already been given (see Fig. 7 in Lecture I).

(*b*) Antibodies which agglutinate at 37° C. but do not bind complement—that is, are non-haemolytic *in vitro*—except when they have a very low titre, bring about removal of red cells in the liver (see case of anti-c with a titre of 128 in saline described by Cutbush and Mollison, 1958), and when they are weak bring about the removal of red cells in the spleen (see case of anti-Mi^a with a titre of 1 in 2 in saline described by Cutbush and Mollison, 1958).

(*c*) Incomplete antibodies which bind complement bring about removal of most or some of the injected red cells from the circulation with a half-time of between two and six minutes (see, for example, Fig. 11 and various cases described by Cutbush and Mollison, 1958). It can be shown by surface counting that most of the red cells are removed from the circulation by the liver.

The pattern of destruction produced by this type of antibody can also be studied by taking red cells from a normal subject, incubating them with serum containing antibody, and then reinjecting them into the donor's circulation and studying their rate of removal from the circulation (using ^{51}Cr as a red-cell label).

Fig. 11 shows the results of two experiments in the same subject, using different amounts of incomplete, complement-binding antibody. As the figure shows, with a larger dose of antibody about 85% of the cells were rapidly removed and with a smaller dose about 30%. These components have been plotted separately in Fig. 12. This shows that the smaller dose of antibody not only caused the destruction of a smaller proportion of cells but also caused a slower rate of destruction.

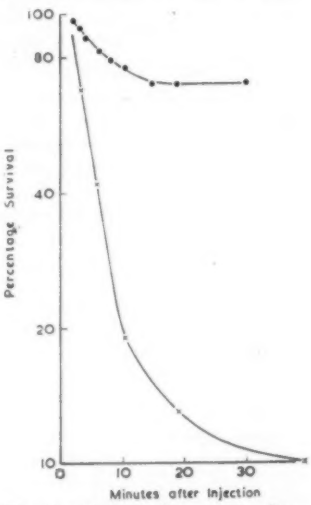

FIG. 11.—Rate of disappearance from the circulation of a subject's own (Fy(a+)) red cells sensitized *in vitro* with a complement-binding anti-Fy^a. ●——● = One volume of red cells incubated with one volume anti-Fy^a. ×——× = One volume of red cells incubated with 2.5 volumes anti-Fy^a. Both curves have two components.

Fig. 12 suggests that removal of red cells from the circulation did not begin for more than 60 seconds after the injection. This apparent lag is in all probability due simply to the method of injecting the cells and of obtaining blood samples; thus, the red cells were injected into a vein in one arm and samples were withdrawn from a superficial vein in the other arm. The rate of mixing observed under these circumstances can be studied by injecting compatible red cells (see Fig. 13), and is found to be distinctly slower than is observed when samples are obtained from the arterial side of the circulation.

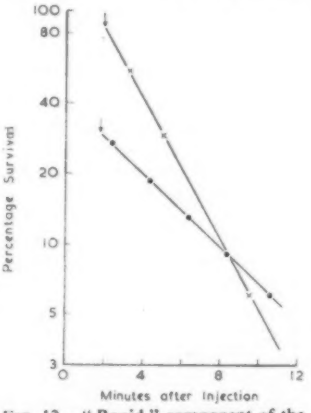

FIG. 12.—"Rapid" component of the curves shown in Fig. 11. The arrows indicate the time after injection at which removal of red cells from the circulation appeared to begin.

(*d*) Incomplete antibodies which do not bind complement bring about removal of red cells predominantly in the spleen. When the antibody is sufficiently potent (titre about 64 or more), blood passing through the spleen may be completely cleared of red cells, so that the rate of removal of cells from the blood stream is equal to the proportion of circulating blood passing through the spleen in a given time. Even when

the titre of antibody is as high as 2,000 there is no increase in the rate of removal of red cells (Mollison and Cutbush, 1955). On the other hand, when the titre is about 1 in 16 the half-time of clearance falls to about 60 to 70 minutes (Cutbush and Mollison, 1958), and when the titre is about 4 the half-time may be several days. Further studies on the quantitative aspects of this type of removal are described in the following section.

In the preceding paragraphs several references have been made to removal of red cells in the liver and spleen. In some of these cases actual surface-counting measurements were made, using apparatus calibrated with models of the liver and spleen (see Mollison and Hughes Jones, 1958). In other cases the sites of removal of the red cells were inferred from the observed half-time of removal of the red cells from the circulation. Thus a half-time of removal of two to four minutes has been found consistently to be associated with removal of red cells predominantly in the liver, and a half-time of 15 to 25 minutes, or, when the antibody is weaker, 60 to 100 minutes, has been found to be associated with removal predominantly in the spleen. Some examples are shown in Table V.

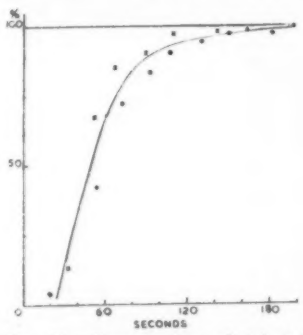

FIG. 13.—Concentration of injected red cells found in blood samples from a superficial vein in one arm at different times after the injection of compatible cells into the other arm. 100% = the concentration attained after complete mixing, based on samples taken 10–20 minutes after injection. Two different populations of red cells (● and ×) labelled with ^{51}Cr and ^{32}P respectively, were injected at an interval of about 30 seconds; in each case the times were expressed as seconds from the midpoint of injection to the midpoint of the sample.

When red cells are fully saturated with complement-binding antibody the half-time of removal (when the volume of red cells injected is of the order of 0.7 ml.) is about 115 seconds (unpublished observations; see also Fig. 12). With knowledge of the total blood volume, the volume of blood cleared of incompatible cells per minute can be calculated. Assuming that incompatible red cells are being removed only by the liver and that the blood is completely cleared of incompatible cells by a single passage through the liver, the volume of blood flowing through the liver can be calculated. In five cases in which calculations were made the average was 1,790 ml. a minute. This is higher than the figure usually accepted for the blood flow through the liver, and suggests that some reticulo-endothelial tissue outside the liver is also removing complement-coated red cells.

TABLE V.—*Examples of Rate of Removal and Main Sites of Destruction Associated with Complement-binding and Non-complement-binding Antibodies. In Each of These Examples Red Cells Were Sensitized with Antibody and then Reinjected Into the Circulation*

Red Cells Sensitized with	Main Component of Curve		Percentage‡ in	
	Half-time (min.)	%	Liver	Spleen
Anti-Fy^a (complement-binding)	2·0	86*	69	13
Anti-Rh (non-complement-binding)	15·0	90†	30	78

* The remaining cells were removed much more slowly.
† 10% of the cells were removed with a half-time of approximately three minutes.
‡ Estimated by surface-counting.

Relationship between Potency of Antibody in Vitro and Rate and Extent of Red-Cell Destruction which it Produces in Vivo

This question has been answered partially by examples already given. It can be explored further by incubating samples of red cells from normal subjects with varying amounts of antibody and reinjecting them, and measuring their rate of removal from the circulation. This can be done conveniently with Rh antibody, and Fig. 14 shows the results of some tests.

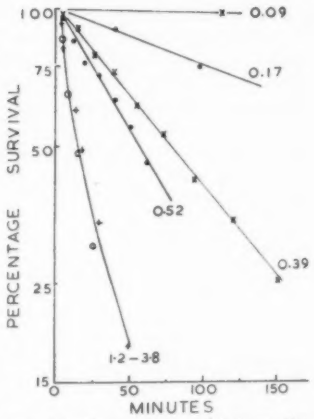

FIG. 14.—Rate of removal from the circulation of Rh-positive red cells sensitized *in vitro* with Rh antibody. The red cells of different normal subjects were incubated with varying amounts of a single batch of gamma-globulin containing a potent incomplete antibody; the figure at the end of each curve refers to the ratio of gamma-globulin to red cells—for example, 0.09 means that 0.09 vol. of gamma-globulin was incubated with 1 vol. of red cells.

A surprising feature of these results is that in some cases at least the rate of destruction does not diminish with time, as would be expected if most of the antibody were coming off the red cells and being distributed amongst the entire (Rh-positive) population. The shape of the curve suggests that, on the contrary, most of the antibody remains attached to the original small sample of red cells for a period of at least 60 minutes after reinjection. The transfer of antibody from sensitized to unsensitized red cells was studied in a series of subsidiary experiments.

Experiments on Transfer of Rh Antibody from Sensitized and Unsensitized Red Cells

The plan of the experiment was to sensitize one volume of Rh-positive red cells (group O) with Rh antibody, then to mix these sensitized red cells with 40 volumes of unsensitized Rh-positive group A red cells. After incubating the mixture for one hour at 37° C. the O cells were separated out by agglutinating the group A red cells. It was found that incubation of the sensitized cells with unsensitized cells for one hour at 37° C. did not greatly diminish the degree of sensitization.

In a second experiment, group A, Rh-positive red cells were sensitized with Rh antibody and then, after thorough washing, mixed with an equal volume of group O, Rh-positive cells. After one hour's incubation at 37° C. the group O cells were extracted, and their degree of sensitization was determined by the direct antiglobulin test. As Table VI shows, when the A cells

TABLE VI.—*Results of Incubating One Volume of Group A, Rh-positive Red Cells, Sensitized with Varying Amounts of Antibody, with an Equal Volume of Unsensitized Group O Rh-positive Red Cells, then Extracting the Group O Cells (Using Anti-A), and Testing them With an Antiglobulin Serum*

Original Reaction of Group A Cells	Final Reaction of Group O Cells
+++	++
+++	+
++	-

were strongly sensitized, the O cells after being incubated with them acquired a positive direct antiglobulin test, but when the A cells were only moderately strongly sensitized the O cells did not acquire any detectable amount of antibody.

These experiments thus show that antibody tends to stay on the red cells with which it originally combines, and that it comes off readily only when it is present in excess. Fig. 15 shows the results of two experiments *in vivo* in one subject. In the first experiment, 0.25 ml. of red cells was labelled with ^{51}Cr, then incubated with 0.95 ml. of gamma-globulin prepared from a serum K. containing Rh antibody. In the second

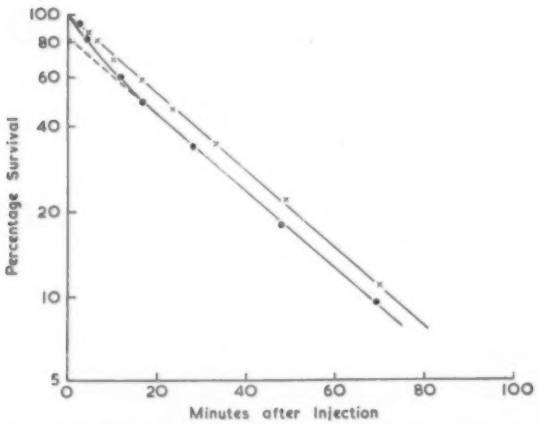

FIG. 15.—Effect of incubating sensitized red cells with an excess of unsensitized red cells on the rate of removal of the sensitized red cells after reinjection. ●——● 0.25 ml. of red cells labelled with ^{51}Cr, then sensitized *in vitro* with 0.95 ml. of gamma-globulin containing Rh antibody before being reinjected. ×——× Red cells labelled and sensitized exactly as above, but then incubated with 5 ml. (20 vols.) of unsensitized red cells before being reinjected.

experiment, 0.25 ml. of red cells was treated in exactly the same way, but was then incubated with 5 ml. (20 volumes) of unsensitized cells before reinjection. As Fig. 15 shows, there was only a very slight diminution in red-cell destruction when the sensitized cells were incubated with unsensitized cells before reinjection.

Effect of Sensitization of Red Cells with Different Amounts of Antibody

When the red cells of different subjects were incubated with varying amounts of anti-Rh (preparation K of gamma-globulin) it was found that the rate of destruction varied with the dose over the range 0.1–1 volume of gamma-globulin to 1 volume of red cells (see Fig. 14). Increasing the dose from 1.2 to 3.8 volumes of gamma-globulin to 1 volume of cells produced no further increase of red-cell destruction—presumably because the rate of red-cell destruction was limited by the rate of blood flow through the spleen (Mollison and Cutbush, 1955; Hughes Jones *et al.*, 1957).

As already mentioned, a striking finding is the steady destruction of the injected cells for a period of one hour or more after reinjection. When the observations were extended for a longer period some change in this pattern was apparent. Thus, Fig. 16 shows that the rate of destruction slows about 5 hours after injection, suggesting that by the end of this time an appreciable amount of antibody has come off the red cells. The red cells which are left in the circulation at the end of this time may survive normally, suggesting that the dose of antibody on their surface has now fallen to a harmless level (see Fig. 17).

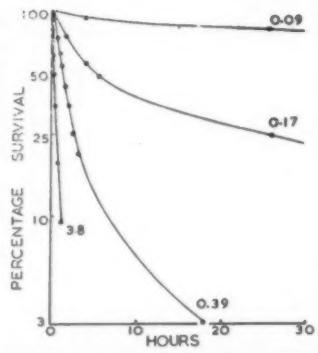

FIG. 16.—Some of the observations shown in Fig. 14 continued over a longer period of time. There is evidence of a change in the rate of destruction four to five hours after injection.

These findings may be used to explain and reconcile some previous observations. For example, Loutit and Mollison (1946) transfused blood from some patients with acquired haemolytic anaemia to normal subjects and found substantially normal survival of the transfused red cells. The donors were only mildly affected, and presumably, therefore, the rate of destruction of transfused cells during the few hours immediately after transfusion was only slightly more rapid than normal. Thereafter one may suppose that by slow redistribution of antibody the amount on the transfused cells fell below the critical amount needed to bring about red-cell destruction, and the remaining cells survived normally. A similar explanation may be applied to the findings of Mollison and Paterson (1949).

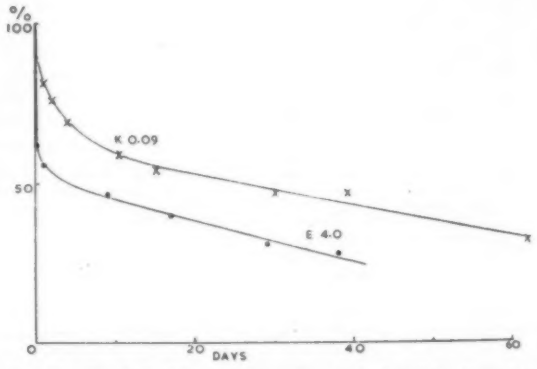

FIG. 17.—Survival of Rh-positive red cells incubated *in vitro* with relatively small amounts of Rh antibody. K 0.09=one volume of red cells incubated with 0.09 volume of gamma-globulin from donor K; the titre of this preparation was 1 in 1,000. E 4.0=one volume of red cells incubated with 4 volumes of gamma-globulin from donor E; the titre of this preparation was 1 in 64.

who transfused normal Rh-positive red cells which had previously been incubated with Rh antibody and found a substantially normal survival, but they added that "although the bulk of the sensitized erythrocytes survived normally" after transfusion "there may have been a fraction which was destroyed more rapidly." Re-examination of their data shows that the greatest amount of incomplete Rh antibody used in any experiment was 120 ml. of serum with a titre of 256, incubated with 260 ml. of red cells. This might be equivalent to about 0.15 ml. of serum with a titre of 1,000 added to 1 ml. of red cells; if so, it would be expected (see Fig. 14) that roughly 20% of the cells would be destroyed within the first hour after transfusion and that thereafter the rest would survive normally.

Similarly, in infants with a positive indirect antiglobulin test but no haematological evidence of red-cell destruction Mollison and Cutbush found that transfused Rh-positive red cells might survive normally even though they took up antibody and gave a positive direct antiglobulin test (quoted in Mollison, 1951, p. 382).

Finally, there are cases in which an apparently normal subject is found to have a positive direct antiglobulin test (of the type inhibited by adding gamma-globulin to the antiglobulin serum) and yet to have a normal red-cell survival (see Mollison, 1956, p. 165). In such cases it may well be that the amount of gamma-globulin on the red cells is below that found in typical cases of acquired haemolytic anaemia. Red cells which have adsorbed sufficient gamma-globulin in the form of Rh antibody to give a moderately strong direct antiglobulin test may still have adsorbed an amount insufficient to bring about an accelerated rate of destruction.

Owren (1948) and Selwyn and Hackett (1949) reported that when red cells were taken from patients severely affected with acquired haemolytic anaemia and transfused to normal subjects 50% or more of the transfused red cells were destroyed within the first day or two, and the remaining cells survived normally. This finding may be compared with some of the curves shown in Figs. 16 and 17; the slowing of the rate of destruction after the first few hours is presumably accounted for by redistribution of antibody.

The data in Fig. 14 give some indication of the amount of antibody which can be expected to produce appreciable red-cell destruction if transfused to an Rh-positive subject. Thus, supposing that an Rh-positive recipient with a red-cell volume of 1,000 ml. is transfused with a bottle of blood containing 200 ml. of plasma with a titre of 256, the amount of red-cell destruction will be expected to be approximately equivalent to that observed if 50 ml. with a titre of 1,000 was injected—that is, a ratio of 0.05 of Rh antibody with a titre of 1,000 to 1 ml. of red cells. As Fig. 14 shows, this will be expected to produce only about 10% of red-cell destruction, but this might be enough, when applied to the whole red-cell mass, to produce transient bilirubinaemia, etc. The conclusion agrees well with observations published by Jennings and Hindmarsh (1958) based on actual transfusions of plasma containing anti-Rh to Rh-positive patients. They found that when 250 ml. of plasma was transfused there was a definite fall in the recipient's haemoglobin concentration only when the titre of Rh antibody was 1 in 128 or more.

Some Practical Applications of a Test in Vivo for Compatibility

Doubts about the interpretation of tests *in vitro* may arise on two counts: (1) doubts about the thermal range of the antibody, and (2) doubts about the specificity of the antibody.

Doubts About Thermal Range of Antibody

As already described, antibodies exist which *in vitro* react with red cells only up to a temperature of 34° C., but are capable of bringing about destruction of transfused red cells. Moreover, antibodies which are active *in vitro* only up to a temperature of approximately 31° C. may bring about destruction of transfused red cells, though at a slower rate. Therefore, when an antibody is encountered which is definitely active at a temperature of 30° C. but only dubiously active at higher temperatures there is bound to be some doubt whether or not the antibody will be capable of bringing about the destruction of transfused red cells.

It might seem that the proper solution in such cases would always be to select for transfusion red cells lacking the relevant antigen, but there are circumstances in which this is difficult to arrange. For example, in patients undergoing certain heart operations in the course of which perfusion with the "heart–lung" machine is to be used, large amounts of fresh blood are required. If a cold agglutinin in the patient's serum is to be taken into account in the selection of donors, preliminary tests on a large number of donors will have to be made, and this may be almost impossible to arrange. Indeed, in such circumstances the only practicable way of obtaining the necessary donors may be to call upon members of the "National Panel" whose full blood groups are known. One should be fairly certain that it is really necessary to take a particular cold agglutinin into account before using such donors. That this is not a hypothetical situation is shown by the fact that in a period of two months at one particular hospital three patients due to undergo heart operations involving perfusion were encountered with anti-P in their serum, active *in vitro* at 30° C. or higher. In each case a test with ^{51}Cr-labelled P-positive cells was performed, using selected "strong" P-positive red cells. In two cases the survival of the cells was absolutely normal, and P-positive blood was used for transfusion without any untoward effects. In the third case there was slow destruction of a proportion of the injected P-positive red cells (15–20% in the first few hours), and it was deemed necessary to use known P-negative donors for transfusion during operation.

In these particular cases hypothermia was not employed. In patients who are to be cooled to about 30° C. it may be necessary to take into account specific cold agglutinins which are active *in vitro* only at temperatures up to 25° C. or 30° C.; but this is speculation, and no experience has yet been obtained in such circumstances.

Doubts About Specificity of Antibody

Two types of case are known in which it is difficult to predict the specificity which an antibody will display *in vivo*. The first is some patients with acquired haemolytic anaemia. Sometimes in these patients the serum displays clear blood-group specificity, as in the case described by Weiner *et al.* (1953). In some of these cases at least it is possible, by carrying out tests with the

patient's serum *in vitro*, to find red cells which will survive very well *in vivo*; that is, much better than the patient's own red cells. An example is shown in Figs. 18 and 19. In this case, when red cells having the same Rh antigens as those of the patient's own red cells were injected, 25% were removed in the first 120 minutes (Fig. 18) and 90% were removed in 24 hours (Fig. 19).

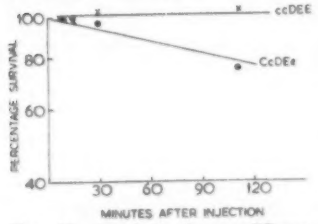

FIG. 18.—Survival of two different types of red cells in the circulation of a patient with acquired haemolytic anaemia. The patient's Rh phenotype was CcDEe, and his serum contained anti-e and anti-C.

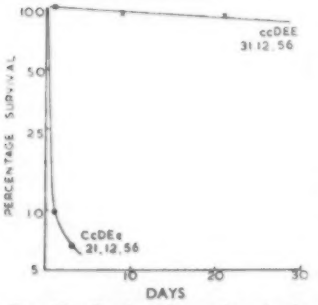

FIG. 19.—Further observations in the patient referred to in Fig. 18. The results for the survival of CcDEe cells injected on December 21, 1956, are simply a continuation of the results shown in Fig. 18. The results for the ccDEE cells refer to an injection given 10 days later.

Red cells lacking the critical antigens were injected at the same time and survived normally for the first 120 minutes; their survival could not be followed satisfactorily for longer because they were labelled with ^{32}P. Ten days later a sample of red cells from the same donor was labelled with ^{51}Cr and the cells were found to survive very well (Fig. 19). It was difficult to assess this second result because the patient was improving rapidly as a result of steroid therapy. In such circumstances more decisive results can be obtained by using methods permitting the simultaneous estimation of the survival of two populations — for example, a combination of differential agglutination for one population and ^{51}Cr labelling for another. An example of this application has been published elsewhere (Mollison, 1959a).

When the serum of a patient reacts with all samples tested it may be worth while to determine by a preliminary test with very small volumes of ^{51}Cr-labelled red cells whether the red cells are not very rapidly destroyed *in vivo* before embarking on a full-scale transfusion.

One other circumstance in which the precise specificity displayed by an antibody cannot readily be determined by tests *in vitro* was described by Cutbush *et al.* (1956). In a patient whose serum contained anti-Le^a group O, Le(a−b+) cells were found to undergo partial destruction (see Figs. 4 and 5 in Lecture I). *In vitro* an interaction between such cells and the patient's serum could be revealed only by the technique of first treating the red cells with an enzyme and then carrying out an indirect antiglobulin test.

Incompatibility without Demonstrable Antibodies

In occasional recipients whose own red cells survive normally, transfused normal red cells fail to survive for the normal length of time. It seems reasonable to describe this as a kind of incompatibility, even though no antibody can be demonstrated. This phenomenon was first described by Loutit, Mollison, and Young (1943), who encountered 4 examples in 35 transfusions. A later survey suggested that the incidence of the phenomenon was about 1 in 20 transfusions (Mollison, 1954).

When ^{51}Cr was introduced as a red-cell label and cross-transfusions of relatively small volumes of red

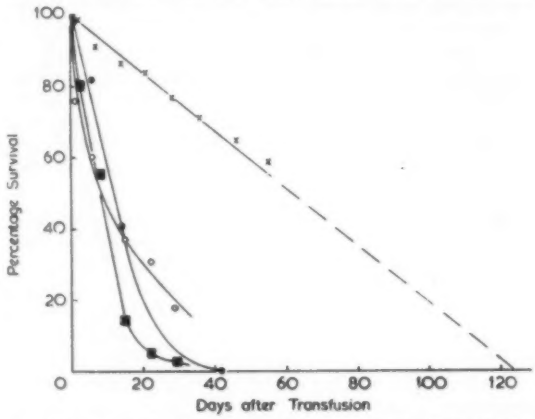

FIG. 20.—Survival of red cells from a normal donor (L. F.) ×——× = Survival of L. F.'s red cells in her own circulation, estimated by ^{51}Cr survival and corrected for Cr elution. ●——● = Survival of L. F.'s cells in recipient I. S., estimated in 1952 by differential agglutination. O——O and ■——■ = Survival of L. F.'s cells in recipient I. S., estimated on two occasions (in 1955) with ^{51}Cr-labelled cells; estimates corrected for Cr elution.

cells were given, the phenomenon was encountered more often (see Adner and Sjölin, 1957). Indeed, it appears that one must expect a diminished survival in about one-third of cases. Thus, Drs. P. L. Adner and S. Sjölin (personal communication) have now found a diminished survival in 13 out of 40 cross-transfusions. In 4 out of the 13 recipients a blood-group antibody could be demonstrated, but in the remaining nine cases no serological incompatibility was apparent. Similarly, Drs. G. S. Eadie and Ivan Brown (personal communication) found a diminished survival in 7 out of 23 cross-transfusions of ^{51}Cr-labelled red cells and failed to find antibodies in most cases. It is not known why this phenomenon is found so much more often with small volumes of ^{51}Cr-labelled red cells than with ordinary transfusions; it is not found when a sample of a subject's own red cells is labelled with small amounts of ^{51}Cr and reinjected into his circulation.

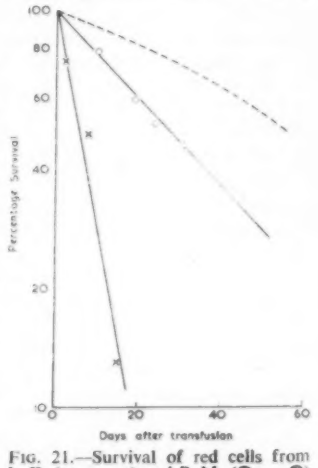

FIG. 21.—Survival of red cells from L. F. (×——×) and P. M. (O——O) in recipient I. S. (cf. Fig. 20, and see also Table VII). The broken line is the curve of normal survival.

Observations in two recipients in whom normal red cells failed to survive normally are shown in Figs. 20–24.

and blood group results in the same cases are shown in Table VII. The first recipient (Figs. 20 and 21) received her first transfusion in 1952—for severe post-partum anaemia. Transfused red cells (from two donors, H.T. and L.F.) were all removed from her circulation in 40 days. Three years later, when she was in normal health, she was given a small injection of red cells from one of the same donors (L.F.), labelled with ^{51}Cr. The red cells were again removed abnormally rapidly, and a third transfusion gave the same result (see Fig. 20). On a further occasion the patient was given red cells from a different donor (P.M.), and these survived distinctly better than those of the first donor (see Fig. 21), although their survival was not strictly normal (possibly because of menorrhagia). The subject's own red cells survived normally in her own circulation. No blood-group antibody, apart from anti-B, could ever be demonstrated in this subject's serum.

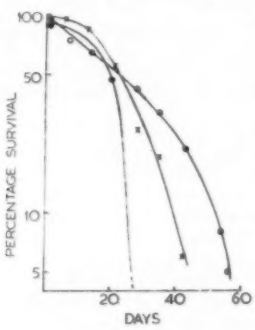

FIG. 22

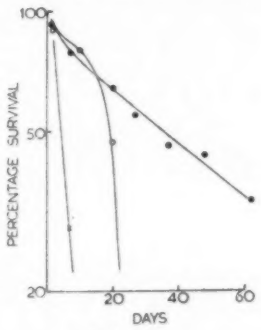

FIG. 23

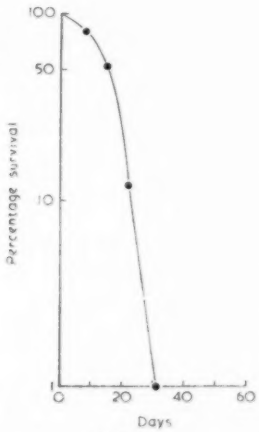

FIG. 24

FIG. 22.—Survival of red cells from a donor (D. B.) after injection into a patient (P. K.) suffering from thalassaemia/haemoglobin C disease (see Table VII). Three tests were made with ^{51}Cr-labelled red cells; the estimates in the figures have been corrected for elution of ^{51}Cr. ●——● = May, 1954. ×——× = August, 1954. O——O = 1957.

FIG. 23.—Further red-cell-survival tests in patient P. K. ●——● = W. R., 1954. ×——× = W. R., 1958. O——O = D. B., 1954. All estimates were made with ^{51}Cr-labelled red cells and corrected for Cr elution.

FIG. 24.—A further red-cell-survival test in patient P. K. Figure shows the survival of red cells from donor J. M. (see Table VII).

In Table VII the blood groups of the recipient and of the various donors are shown. The only antigen possessed by L.F. which was foreign to the recipient was the Rh antigen E, and it will be seen that this antigen was also possessed by the donor H.T., whose cells also survived badly, and was not possessed by P.M., whose red cells survived well. It is thus tempting to suppose that in this case the red-cell destruction was due to a very weak anti-E, although repeated attempts to demonstrate this antibody in the recipient's serum failed.

Figs 22, 23, and 24 show observations in a patient (P.K.) with thalassaemia/haemoglobin C disease who was severely anaemic. Some details of this case have been published previously (Mollison, 1956, p. 355, Fig. 55). The red cells of one donor (D.B.) survived poorly on several occasions: sometimes survival was normal or almost normal for the 10 to 15 days after transfusion, and the cells were then rapidly eliminated (see Fig. 22). Red cells from another donor (W.R.) survived well on the first two occasions on which they were used (in 1954), but when used again (in 1958) they were eliminated very rapidly (Fig. 23). No antibodies against the cells of any of the donors could ever be demonstrated in the patient's serum. Some of the survival curves were distinctly convex, suggesting the possibility that an immune response developed 10 to 20 days after transfusion (see Figs. 22–24).

As Table VII shows, red cells from three donors were transfused in 1954. The red cells of donors A.G. and W.R. survived well, whereas those of D.B. survived poorly. The only red-cell antigen which D.B. was known to have which was not present in the red cells of the other two donors or the recipient was the Rh antigen C. However, the rapid destruction of transfused red cells by this recipient could not have been due solely to a very weak anti-C, since the red cells of donor M.S., who was C-negative, were rapidly eliminated.

The occurrence of this form of incompatibility hardly constitutes a danger in transfusion, since the red cells are destroyed too slowly to cause any untoward effects.

TABLE VII.—*Blood Groups of Donors and Recipients in Two Cases in Which Transfused Red Cells Failed to Survive Normally, although no Blood-group Antibody could be Demonstrated*

			Blood Groups*						Red-cell† Survival (Days)	Year of Study	Volume of Red Cells Injected (ml.)
Case 1	Recipient I.S.		A_2	CcDee	MN	S+s+	Le(a+b−)	Fy(a+)	Jk(a+b+)	(Own cells normal)		
(Figs. 20 and 21)	Donors	H.T.	O	ccDEe	MN	S+	Le(a−b+)	Fy(a−)		40	1952	110
		L.F.	A_1	CcDE	N	S−s+	Le(a−b+)	Fy(a+)		40	1952	70
										40	1955	5
		P.M.	A_2	CcDee	MN	S+	Le(a−b−)	Fy(a−b+)	Jk(a−b+)	80–100	1955	6
Case 2	Recipient P.K.		O	ccDEe	N	S+	Le(a−b+)	Fy(a−)		(Own cells reduced)‡		
(Figs. 22, 23, and 24)	Donors	D.B.	O	CcDEe	N	S−	Le(a−b+)	Fy(a+)	Jk(a+b−)	30	1954	10
										50	1954	8
										60	1957	3
		A.G.	O	ccddee	MN	S+	Le(a−b+)	Fy(a+)		120	1954	200
		W.R.	O	ccddee	MN	S−	Le(a−b+)	Fy(a+)		120	1954	200
										120	1954	6
										10	1958	4
		M.S.	O	ccDEe	MN	S−	Le(a−b+)	Fy(a+)		40	1958	7
		J.M.	O	CCDee	MN	S+	Le(a+b−)	Fy(a−)	Jk(a−)	35	1958	7

* All donors and recipients were P +, Lu(a −), K −. † Approximate time for elimination of all injected red cells. ‡ Patient affected with thalassaemia/haemoglobin C disease.

Summary

We are now very near to being able to predict from tests *in vitro* whether a given sample of red cells will undergo rapid destruction if transfused to a particular patient and, if so, how rapid destruction will be, whether it will involve all or only some of the transfused red cells, whether it will be predominantly intravascular or extravascular, and, if extravascular, whether it will occur predominantly in the liver or the spleen.

Further observations, particularly in patients whose serum contains "cold" specific iso-agglutinins, are needed to define still more clearly the relationship between the thermal range of an antibody *in vitro* and its power to bring about red-cell destruction *in vivo*. The more academic problem of the relatively slow destruction, in particular subjects, of transfused red cells in the absence of demonstrable antibodies still awaits solution.

I wish to thank Professor A. C. Dornhorst for many helpful discussions; Dr. W. J. Jenkins for permission to use his serological findings in the case referred to in Figs. 18 and 19; Dr. E. E. Pochin for permission to investigate a patient under his care; Miss Marie Cutbush (now Mrs. Crookston), B.Sc., for help with some of the experiments on the removal of sensitized red cells from the circulation; Miss Margaret Polley, B.Sc., for carrying out the experiments on the transfer of antibody *in vitro*; Miss Norah Ramsden for identifying the anti-O; Dr. Dorothy Parkin for blood-group determinations; and Miss Denise Hunter and Mrs. Ann Weedon for technical assistance.

REFERENCES

Adner, P. L., and Sjölin, S. (1957). *Scand. J. clin. Lab. Invest.*, **9**, 265.
Ashby, Winifred (1919). *J. exp. Med.*, **29**, 267.
Aveling, J. H. (1873). *Obstet. J.*, **1**, 542.
—— (1874). Ibid., **2**, 223.
Blundell, J. (1824). *Researches Physiological and Pathological*. London.
—— (1828–9). *Lancet*, **1**, 431.
Chaplin, H., jun. (1959). *Blood*, **14**, 24.
Christian, R. M., Stewart, W. B., Yuile, C. L., Ervin, D. M., and Young, L. E. (1951). *Blood*, **6**, 142.
Coombs, R. R. A., and Mourant, A. E. (1947). *J. Path. Bact.*, **59**, 105.
—— —— and Race, R. R. (1945). *Brit. J. exp. Path.*, **26**, 255.
Crawford, H., and Mollison, P. L. (1951). *Lancet*, **2**, 955.
Crile, G. W. (1909). *Hemorrhage and Transfusion*. Appleton, New York and London.
Cutbush, Marie, Crawford, H., and Mollison, P. L. (1955). *Brit. J. Haemat.*, **1**, 410.
—— Giblett, Eloise R., and Mollison, P. L. (1956). Ibid., **2**, 210.
—— and Mollison, P. L. (1958). Ibid., **4**, 115.
Dacie, J. V. (1951). *Lancet*, **2**, 954.
—— (1957). *Proc. roy. Soc. Med.*, **50**, 647.
—— Crookston, J. H., and Christenson, W. N. (1957). *Brit. J. Haemat.*, **3**, 77.
Denis, J. (1667–8). *Philos. Trans.*, **1**, 621.
Fagge, C. H., and Pye-Smith, P. H. (1891). *Textbook of the Principles and Practice of Medicine*, 3rd ed. Churchill, London.
Fairley, N. H. (1941). *Quart. J. Med.*, **10**, 95.
Gray, S. J., and Sterling, K. (1950). *J. clin. Invest.*, **29**, 1604.
Hughes Jones, N. C., Mollison, P. L., and Veall, N. (1957). *Brit. J. Haemat.*, **3**, 125.
Jandl, J. H., Jones, A. R., and Castle, W. B. (1957). *J. clin. Invest.*, **36**, 1428.
Jennings, C. E. (1883). *Transfusion*, 2nd ed. Baillière, Tindall and Cox.
Jennings, E. R., and Hindmarsh, Corinne (1958). *Amer. J. clin. Path.*, **30**, 302.
Landois, L. (1875). *Die Transfusion des Blutes*. Vogel, Leipzig.
Landsteiner, K. (1901). *Wien. klin. Wschr.*, **14**, 1132.
—— and Levine, P. (1928). *J. exp. Med.*, **47**, 757.
—— and Wiener, A. S. (1941). Ibid., **74**, 309.
Levine, P. (1944). *Exp. Med. Surg.*, **2**, 36.
—— Burnham, L., Katzin, E. M., and Vogel, P. (1941). *Amer. J. Obstet. Gynec.*, **42**, 925.
—— and Stetson, R. E. (1939). *J. Amer. med. Ass.*, **113**, 126.
Loutit, J. F., and Mollison, P. L. (1946). *J. Path. Bact.*, **58**, 711.
—— and Young, I. Maureen (1943). *Quart. J. exp. Physiol.*, **32**, 183.
Lower, R. (1665–6). *Philos. Trans.*, **1**, 353.
Mollison, P. L. (1951). *Blood Transfusion in Clinical Medicine*, 1st ed. Blackwell, Oxford.
—— (1954). *Lectures on The Scientific Basis of Medicine, 1952–53*, **2**, 269. London.
—— (1956). *Blood Transfusion in Clinical Medicine*, 2nd ed. Blackwell, Oxford.
—— (1959a). *Brit. med. Bull.*, **15**, 59.
—— (1959b). Ibid, **15**, 92.
—— and Cutbush, Marie (1955). *Lancet*, **1**, 1290.
—— and Hughes Jones, N. C. (1958). *Vox Sang.*, **3**, 243.
—— and Paterson, J. C. S. (1949). *J. clin. Path.*, **2**, 109.
—— and Polley, Margaret J. (1959). *Immunology*. In press.
—— and Thomas, Ann R. (1959). *Vox Sang.*, **4**, 185.
Ottenberg, R., and Kaliski, D. J. (1913). *J. Amer. med. Ass.*, **61**, 2138.
Owren, P. A. (1948). *Blood*, **3**, 231.
Ponfick, Prof. (1875). *Virchows Arch. path. Anat.*, **62**, 273.
Race, R. R. (1944). *Nature (Lond.)*, **153**, 771.
Renton, P. H. (1952). Ibid., **169**, 329.
Schäfer, E. A. (1880). *Trans. Obstet. Soc. Lond.*, **21**, 316.
Selwyn, J. G., and Hackett, W. E. R. (1949). *J. clin. Path.*, **2**, 114.
Streng, O. (1930). *Acta path. microbiol. scand.*, Suppl. 3, p. 411.
Todd, C., and White, R. G. (1911). *Proc. roy. Soc. B*, **84**, 255.
Vogel, P., Rosenthal, N., and Levine, P. (1943). *Amer. J. clin. Path.*, **13**, 1.
Weiner, W., Battey, D. A., Cleghorn, T. E., Marson, F. G. W., and Meynell, M. J. (1953). *Brit. med. J.*, **2**, 125.
Wiener, A. S. (1941). *Arch. Path. (Chicago)*, **32**, 227.
—— (1944). *Proc. Soc. exp. Biol. (N.Y.)*, **56**, 173.

CASE OF CARBON-MONOXIDE POISONING WITH COMPLICATIONS

SUCCESSFUL TREATMENT WITH AN ARTIFICIAL KIDNEY

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The inhalation of carbon monoxide is a common method of attempted suicide, but nerve damage and muscle necrosis with acute renal failure are a rare complication. Reports have been published of mental and neurological sequelae from carbon-monoxide poisoning; among records of cases that survive the usual fatal long exposure to the gas (Shillito *et al.*, 1936; Adams *et al.*, 1953) we have been unable to find any mention of myonecrosis and wasting due to neuropathy occurring in the same patient.

Table I gives a summary of the cases with muscle necrosis and renal failure we have traced in the literature.

The following case is published in view of its rarity and because, in spite of many serious hazards, treatment with an artificial kidney (Kolff twin-coil) was successful. As a result of the carbon-monoxide poisoning the patient had muscle necrosis, acute renal failure, mental changes, a radiculomyelitis of L 2 to 5, and probably myocardial damage.

TABLE I.—*Muscle Necrosis and Renal Failure*

Authors	Cases	Causes	Renal Failure	Results
Günther (1921)	1	Carbon monoxide	Yes	Died
Mautner (1955)	1	" "	Oliguria 4 days. Blood urea up to 180 mg./100 ml.	Recovered
Fahlgren *et al.* (1957)	5	Alcoholism and barbiturates	Yes (2 cases)	Both died (one on way for treatment by artificial kidney)
Loughridge *et al.* (1958)	1	Carbon monoxide	Yes	Died (just prior to haemodialysis)

Case Report

A married woman aged 35 attempted suicide by inhalation of carbon monoxide in the early hours of September 19, 1958. She sealed herself in her kitchen, turned on all the gas-cooker taps, and sat on a chair with her head resting on her arms on a table. When found by her husband at 7.30 a.m. on the 19th exposure was estimated to have lasted 6½ hours. It took three hours for her to regain consciousness. When she was found her position on the chair was as shown in Fig. 1. She complained of severe pain in her back and lower limbs on recovering consciousness and was continually crying out.

On September 20 (2nd day) her doctor referred her to the local hospital for *x*-ray examination of her spine on account of persistent severe back pain. As the findings were doubtful she was admitted the same day to the Wingfield-Morris Hospital, Oxford, with a suspected spinal fracture. The next day she passed no urine. *X*-ray examination of her spine showed it to be normal.

On September 22 (4th day) she was transferred to the Radcliffe Infirmary, where her urinary output was only about 120 ml. in 24 hours and the blood urea 200 mg./100 ml. No myoglobinuria was found. Muscle necrosis was suspected because of the continued back pain and tenderness.

She was transferred to the renal unit at Halton on the 23rd.

On admission she was fully conscious, and was groaning and shouting because of headaches and pain, with extreme tenderness in the muscles of her back and lower limbs. She was very emotional. Examination revealed acute tenderness of all muscles, particularly over the lower thorax, thighs, and calves. There was a swelling (5 by 4 in.: 12.5 by 10 cm.) of the right paravertebral muscles over the line of the 10th rib. This was exceptionally tender, there being superficial pitting oedema. Reflexes were absent in both knees, diminished in the ankles, and equivocal in the plantars. There was gross weakness of the back and lower-limb muscles. Urine volume was 100 ml./24 hours, blood urea 238 mg./100 ml., and serum potassium 5.3 mEq/l. During the next 48 hours she had intermittent generalized epileptiform fits.

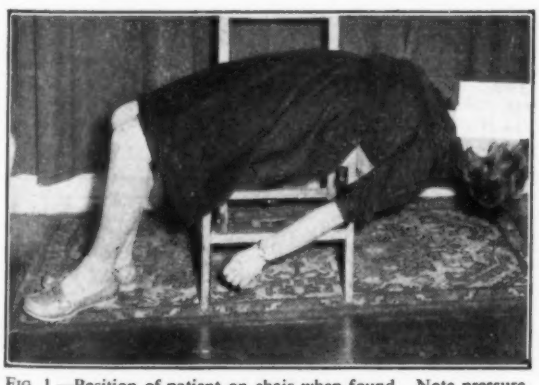

FIG. 1.—Position of patient on chair when found. Note pressure line across lower thorax posteriorly.

Conservative treatment for acute renal failure was begun and, in view of the known dangers of severe hyperkalaemia, included " resonium-A " (an ion-exchange resin) by rectum. Fluid was administered orally as water and glucose most of the time, with only occasional superficial venous infusions of 5% glucose.

Fig. 2 shows the progress with regard to urine volume, blood urea, and dialyses. The patient was difficult to manage because of emotional instability and bouts of overbreathing, twitching, and screaming. Fig. 3 depicts the serum-potassium levels and the effect of large amounts of resonium-A per rectum. It will be seen that haemodialysis was carried out on September 27 (9th day) for six hours, because of anticipation of a sudden hyperkalaemia.

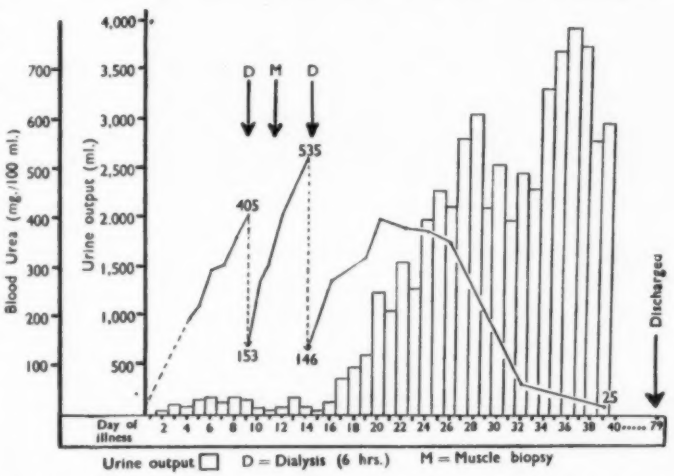

FIG. 2.—Progress during period of oliguria and diuresis, showing blood urea falling during each dialysis.

Muscle biopsy was performed on September 29 (11th day) at the site of the tender swelling on the back (a second such area had occurred by this time, adjacent to the one described).

Histological examination (Wing Commander R. M. Cross) revealed sections of striated muscle with considerable change in normal appearance. Some of the nuclei showed degenerative changes and the majority of them had died. There was variable loss of striation and many had a granular appearance. There was little chronic inflammatory-cell response present. The appearances confirmed the diagnosis of muscle necrosis.

Fig. 4 shows the muscle necrosis. On October 2 the second dialysis was performed for six hours mainly because

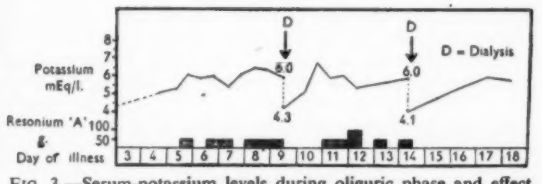

FIG. 3.—Serum-potassium levels during oliguric phase and effect of rectal resonium-A and dialysis.

of clinical deterioration, and during this dialysis the patient developed hypotension, requiring noradrenaline, which we were unable to withdraw for 18 hours. Prior to this, E.C.G.s had shown some depression of the ST segments in the limb leads and leads V3 to 7. We thought that there was some myocardial damage and that the profound hypotension might have been associated with this.

On October 8 (20th day) a diuresis began (a urine volume of over 1 litre in 24 hours), and during a period of six days supplements of potassium totalling 378 mEq were required because of the excessive loss of this ion in the urine. In the oliguric phase (20 days) she was given resonium-A to a total of 600 g. by rectum to reduce the hyperkalaemia, as shown in Fig. 3. Her blood urea reached the normal figure of 25 mg./100 ml. on October 27 (39th day).

FIG. 4.—Low-power photomicrograph of necrosed muscle.

Neurological Examination

On October 13 (25th day) a full neurological examination was made; the findings were as follows:

The patient was correctly orientated, but felt guilty about her behaviour and wept easily. She had a poor memory for recent events, a digit span of seven numbers, and a good knowledge of current affairs; she performed the serial seven test in two minutes with one error, and repeated the Babcock test sentence with one error. The cranial nerves and upper limbs were normal. The abdominal movements were normal; abdominal reflexes were absent in the lower quadrants. There was marked weakness and tenderness of the erector spinae muscles. The lower limbs were symmetrically affected. Power was grossly reduced in the quadriceps, which were wasted, and to a less extent power was reduced in the antero-lateral muscle group and the calf muscles. Tone was normal at the hips and knees; the knee-jerks were absent; the ankle-jerks were increased, with ankle clonus and extensor plantar responses. There was bilateral symmetrical blunting of sensation in all modalities in the dermatomes supplied by L 2–5 roots. There was also blunting of sensation over the sacrum where she had been lying across the chair during coma. The lower dermatomes and cauda equina were spared. The electromyogram and strength/duration curves confirmed that the lower-limb weaknesses were due to lower-motor-neurone lesions. There was transient urinary and rectal incontinence. The cerebrospinal fluid on November 25 showed 90 mg. of protein per 100 ml.

There had been a gradual recovery by mid-December. Sensation was still blunted over a small area on the front of the thighs; the knee-jerks were absent and the plantar responses extensor. Power in the lower limbs and spine had greatly improved, so that she could walk unaided for half a mile. Serial examination of the strength/duration curves showed recovery to normal within two months (Figs. 5 and 6). Sphincters had recovered.

Owing to the neurological sequelae it was not until December 6 (79th day) that she was fit to be discharged home.

When seen as an out-patient at Halton on February 4, 1959, her physical condition had greatly improved. The knee-jerks had returned and the plantar responses were flexor. Power and muscle bulk were 90% recovered. Sensation was only slightly impaired over the front of the thighs. Her mental state was normal. The Hb was 96%. *x*-ray examination of her back muscles showed no calcification. Renal-function tests will be performed at a later date, but her blood urea was 20 mg./100 ml., urinary urea 1.8 g./100 ml., and output about 1,500 to 2,000 ml. in 24 hours.

We consider the mental symptoms were a mild toxic psychosis. The strength/duration curves in the lower-limb muscles, the reflex changes, and the loss of sensation in the associated nerve roots all point to a radiculomyelitis as the cause of the muscle-wasting in the lower limbs.

Discussion

Muscle Necrosis

Apart from trauma, muscle necrosis occurs from anoxia due to carbon monoxide, barbiturates (Touzé and Thierry, 1952), barbiturates and alcoholism (Fahlgren *et al.*, 1957), severe heart failure (Adams *et al.*, 1953), and general anaesthesia (Gordon and Newman, 1953). Of the acute myonecrosis following carbon-monoxide poisoning Adams *et al.* (1953) write: "Anoxaemia, if sufficiently severe, may cause necrosis of muscle. We have observed lesions of this kind in the heart and skeletal limb muscles of humans who have survived for 24–48 hours after being subjected to prolonged anoxia in circulatory collapse." These authorities imply that carbon monoxide myonecrosis is secondary to prolonged pressure and is confined to muscles laid upon during anoxia. We would stress that pressure is important only in causing local increase of anoxia and thereby the actual site of necrosis. The most sensitive part of a limb to oxygen lack is the extremities, and carbon-monoxide myonecrosis has been reported symmetrically in the hands and feet (Laignel-

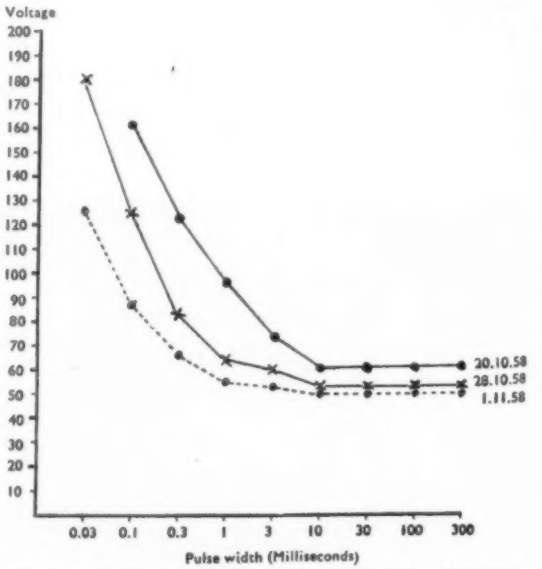

FIG. 5.—Left vastus medialis muscle: strength/duration curve showing a normal response on November 1, 1958.

Lavastine and Alajouanine, 1921). Heart muscle can also be damaged by carbon-monoxide poisoning (Beck and Suter, 1938; Hadley, 1952), as we believe occurred to a small extent in this case.

It is important to remember that necrosis of skeletal muscle can occur with alcoholism. One of the patients of Fahlgren *et al.* (1957) in renal failure developed a swelling of his right arm and shoulder with superficial oedema. Muscle necrosis was found at necropsy. In retrospect we believe necrosis was probably present in a man aged 26 admitted to our renal unit in 1958 in acute renal failure following acute alcoholism (he had infantile hemiplegia and was an epileptic). He had been thrown out of a London public-house and was found lying on his right side and arm in the gutter. He developed a swelling of his right arm from shoulder to elbow which was very tender and took three weeks to subside. There was no bruising. His blood urea rose rapidly to 580 mg./100 ml. in eight days, he was dialysed once, and recovered; muscle biopsy was not done.

Neurological Sequelae

The incidence of nerve damage in carbon-monoxide poisoning is difficult to calculate. If the transient Babinski sign and minimal nystagmus are taken as evidence of nerve damage, then the condition is common; thus Meigs and Hughes (1952) found nerve damage in 79% of 105 hospital cases. Shillito *et al.* (1936) found among the records of 21,000 cases only 43 neuropathies (0.2%), but he listed only well-established lesions.

The histological changes in nerve tissue poisoned by carbon monoxide are those of anoxia (Kinnier Wilson, 1954). Whether the oxygen lack is anaemic, anoxic, or stagnant, the damage wrought in the cells is the same. Direct histotoxic damage to nerve by carbon monoxide was disproved by culturing neuroblasts in 70% carbon monoxide (Haggard, 1922). The concentration of carbon monoxide necessary to inhibit oxidase systems is much higher than the toxic dose (Crisler, 1935). The neuro-histology of "delayed" cases is different and merits comment. Courville (1957) reviewed 22 necropsies. The average time between poisoning and death was 48 days. The pathology was similar in all cases. Extensive confluent zones of perivascular demyelination occurred in the central white matter of the hemispheres. The immediately subcortical white matter was spared. In the demyelinated zones capillaries were reduced in number, arterioles could no longer be identified, and oligodendrocytes were sparse.

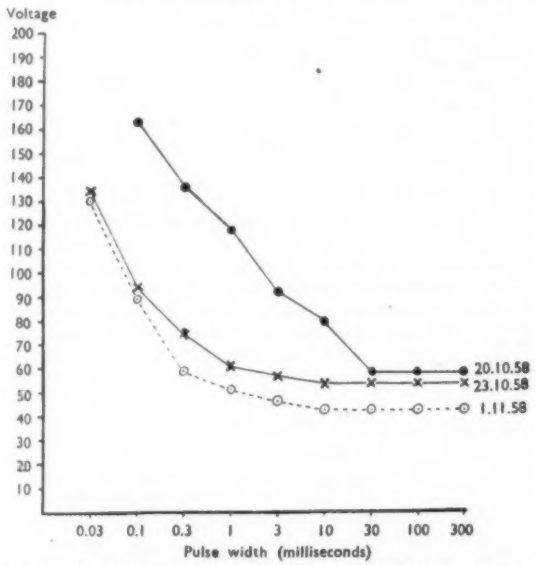

FIG. 6.—Left gastrocnemius muscle: strength/duration curves showing a normal response on November 1, 1958.

Damage to nerve tissue may result in psychiatric, neurological, or mixed syndromes. Cases may be classified as immediate or delayed according to whether symptoms arise within a day or two of return to consciousness or some weeks later. Lesions have been recorded in all parts of the nervous system in carbon-monoxide poisoning. Cortical damage has resulted in hemiplegia, monoplegia, aphasia, hemianopsia, cortical blindness, etc. Commonly, these symptoms are transient. Diffuse cortical damage gives rise to dementia: all gradations are seen, from a minor constructional apraxia to complete mindlessness. Gerstmann's syndrome is common during recovery from confusion (Allison, 1956).

Traditionally the basal ganglia are considered a locus minoris resistentiae to carbon monoxide, and Parkinsonism the commonest sequela. Analysis of the cases of Shillito *et al.*, one of the largest groups in the literature, makes this view dubious. Table II shows that

TABLE II.—*Sequelae in Carbon-monoxide Poisoning Among* 21,143 *Cases* (*Shillito et al.*, 1936)

No. showing muscular hypertonia (increased reflexes, perhaps clonus and positive Babinski sign)	9
No. showing hypertonia and peripheral neuritis	5
,, ,, Parkinsonism	4
,, ,, ,, and some degree of peripheral neuritis	1
,, ,, peripheral neuritis only	4
,, ,, no neurological sign	10
,, dying before complete neurological examination	10
	43

of 43 survivors from carbon-monoxide poisoning with neurological damage, five had Parkinsonism. But the chance of extrapyramidal symptoms getting better is slight. Only one case of Parkinsonism cleared up, while all but four of 28 other neurological cases lost their symptoms. Because anoxic Parkinsonism rarely shortens life, is rarely cured, and is recognizable at a glance, it may be reported too often. Other clinical pictures resulting from anoxic damage to the basal ganglia are rare. Pupillary changes and nystagmus often tell of brain-stem lesions (Meigs and Hughes, 1952). In the cord, paraplegia has been noted (Zipf, 1937). Radicular lesions are less common than neuropathies (Renfert and Drew, 1955). Peripheral neuropathies are sometimes complicated by burning pain. Epilepsy is rare but may be intractable.

The mildest psychic changes in carbon-monoxide poisoning may be confined to a transient mood change, often in keeping with the life situation, as in the case above. Temporary uncovering of anti-social traits such as aggressiveness may last some months. The severe psychiatric syndrome is an organic toxic-confusional state: confusion, amnesia, disorientation, lack of judgment, and mood changes are evident, while hallucinations and other schizophrenic symptoms are uncommon.

The neurological deficit after carbon-monoxide poisoning is usually apparent within a few days of exposure. The delayed cases may occur weeks later: usually, recovery has not been complete when the

relapse occurs. The neurological lesions are in no way distinctive, and may affect any part of the nervous system. There is nothing to distinguish the toxic psychosis of carbon monoxide from that due to any other noxious process unless it be the history of exposure and the coincidental neurological damage.

Carbon monoxide has long enjoyed an evil reputation for causing irreparable mental and nervous syndromes. Yet of 43 survivors with severe neurological or psychiatric disorders all but 10 recovered (Shillito *et al.*, 1936). Recovery usually ceases within two years but may continue up to this time, so that there is no reason to give a gloomy outlook in the early acute case. The delayed case is a different matter. In two series "pseudorecovery," as this is sometimes called, has been followed by death in half the cases. Treatment of the neurological damage is confined to reassurance, rest, passive movement, and prevention of stretching the paretic muscles. Passive full-range movement of necrosed muscles is essential to prevent Volkmann's contracture and calcification. The treatment of psychiatric syndromes should be supportive psychotherapy.

Renal Failure

When acute renal failure has occurred with muscle necrosis the constant danger is the hyperkalaemia with a sudden rise to fatal levels. It can be seen from Fig. 3 that, in the case reported, large amounts of resonium-A only just controlled the hyperkalaemia temporarily. Dialysis in these cases should be carried out earlier than the clinical state would indicate and before the serum potassium has reached 7 mEq/l., or the serum bicarbonate 12 mEq/l. Serum-potassium levels were estimated twice daily together with the occasional E.C.G., though the latter we have found to be of less assistance in the assessment.

With this type of case we would go so far as to recommend transfer to a unit where the technique for haemodialysis is available, as soon as the possibility of muscle necrosis is suspected.

No myoglobinuria was found in this patient, as it was only on the third day that a search was made. The renal lesion was acute tubular necrosis, and it is anticipated that the patient will regain normal renal function within 12 months. The management of a difficult case of this nature is the same as with any acute renal failure with much tissue breakdown. Our experience has shown the necessity for the most careful and frequent assessment at the bedside, with all the facts assembled at least twice a day. Otherwise these patients can slip out of control rapidly. One should be prepared to dialyse early even though this may mean an extra dialysis. This is made evident by the reports of Fahlgren *et al.* (1957) and of Loughridge *et al.* (1958).

Summary

A case is described of carbon-monoxide poisoning with the following complications — skeletal-muscle necrosis, probable myocardial necrosis, acute renal failure, mental changes, and a radiculomyelitis of L 2–5.

The details of conservative management and haemodialysis (twice) by a Kolff twin-coil artificial kidney are given. The literature concerning muscle necrosis and renal failure, with the neurological sequelae, is reviewed.

We thank Wing Commander R. M. Cross and his staff of the R.A.F. Institute of Pathology for the histology, photomicrograph, and biochemistry; Squadron Leader A. Lough and his staff for the physiotherapy and strength/duration curves; Wing Commander P. R. Travers and Flight Lieutenant R. G. Lascelles for their assistance; the nursing staff of the Princess Mary's R.A.F. Hospital for their excellent care; and the Director-General of Medical Services, Royal Air Force, for permission to publish.

References

Adams, R. D., Denny-Brown, D., and Pearson, C. M. (1953). *Diseases of Muscles.* Hoeber, New York; Cassell, London.
Allison, R. S. (1956). *Proc. roy. Soc. Med.*, **49**, 609.
Beck, H. G., and Suter, G. M. (1938). *J. Amer. med. Ass.*, **110**, 1982.
Courville, C. B. (1957). *J. nerv. Ment. Dis.*, **125**, 534.
Crisler, G. (1935). *Amer. J. Physiol.*, **110**, 580.
Fahlgren, H., Hed, R., and Lundmark, C. (1957). *Acta med. scand.*, **158**, 405.
Gordon, B. S., and Newman, W. (1953). *J. Bone Jt Surg.*, **35A**, 764.
Günther, H. (1921). *Z. klin. Med.*, **92**, 41.
Hadley, M. (1952). *Brit. Heart J.*, **14**, 534.
Haggard, H. W. (1922). *Amer. J. Physiol.*, **60**, 244.
Hedinger, C. (1948). *Dtsch. Z. Chir.*, **20**, 476.
Laignel-Lavastine and Alajouanine (1921). *Bull. Soc. méd. Hôp. Paris*, **45**, 484.
Loughridge, L. W., Leader, L. P., and Bowden, D. A. L. (1958). *Lancet*, **2**, 349.
Mautner, L. S. (1955). *A.M.A. Arch. Path.*, **60**, 136.
Meigs, J. W., and Hughes, J. P. W. (1952). *A.M.A. Arch. industr. Hyg.*, **6**, 344.
Renfert, H., and Drew, A. (1955). *Ann. intern. Med.*, **42**, 942.
Shillito, F. H., Drinker, C. K., and Shaughnessy, T. J. (1936). *J. Amer. med. Ass.*, **106**, 669.
Touzé, J., and Thierry, M. (1952). *Bull. Soc. méd. Hôp. Paris*, **68**, 971.
Wilson, S. A. Kinnier (1954). *Neurology*, 2nd ed., edited by A. N. Bruce. Butterworth, London.
Zipf, H. (1937). *Dtsch. Z. Nervenheilk.*, **142**, 39.

ARTIFICIAL RESPIRATION AND AN ARTIFICIAL KIDNEY FOR SEVERE BARBITURATE POISONING

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Most patients admitted to hospital suffering from barbiturate intoxication will recover provided that steps are taken to keep the airway clear, to maintain fluid balance, and to prevent hypostatic pneumonia (Nilsson, 1951; Locket and Angus, 1952). Some authors favour the use of analeptics such as picrotoxin and bemegride ("megimide") (Shulman *et al.*, 1955; Koppanyi and Richards, 1958), but there is little evidence that these drugs play any major part in the recovery of the patients (Eckenhoff and Dam, 1956). The essential of treatment, however, should be to maintain adequate respiration of the patient and an adequate circulation. The problem is similar to that of managing a deeply anaesthetized patient; the only difference is that the person with barbiturate intoxication usually remains in coma for a longer time. It may be possible to shorten the duration of coma substantially by dialysing

with an artificial kidney some of the ingested barbiturate out of the body (Alwall *et al.*, 1952; Walsh *et al.*, 1952).

A case, in which there was no renal failure, is described of recovery from an otherwise fatal dose of butobarbitone. Artificial respiration, using a mechanical pump, was employed to ventilate the lungs when spontaneous respiration had stopped; the blood-pressure being unrecordable, L-noradrenaline was used to maintain the circulation. An artificial kidney was brought to the patient and used to dialyse a substantial amount of barbiturate from the body.

Case Report

A 30-year-old man was admitted to the Radcliffe Infirmary as an emergency case on September 10, 1958. That day his wife had wakened at about 6.30 a.m. and had found it impossible to rouse him. At first she paid little attention to this, but became worried when, 20 minutes later, he still could not be awakened. She then noticed that he looked blue and was breathing noisily. On being sent for, the family doctor, thinking that the patient had suffered a cerebrovascular catastrophe, sent him to hospital, where he arrived at 10 a.m. He was deeply unconscious. Slight cyanosis was present, but this was relieved when a metal Waters airway was introduced into the mouth and mucus aspirated from the pharynx. He then looked quite peaceful and was breathing quietly; the body and limbs were warm. His axillary temperature was 96.4° F. (35.8° C.), pulse 112, and blood-pressure 90/60 mm. Hg. There was no neck stiffness, the pupils were moderately dilated and did not react to light. The tendon reflexes were absent, except for both biceps brachialis, from which a flicker could be obtained, and no plantar response could be elicited.

In view of the coma, in the absence of any localizing signs in the central nervous system, his good general condition, and the absence of evidence of other disease, a provisional diagnosis of barbiturate intoxication was made. After discussion with his wife she returned home and discovered that a box of butobarbitone ("soneryl") tablets which had been in the house for over two years was missing.

A stomach-tube was passed, its contents were aspirated, and he was catheterized. In the meantime blood analysis showed the presence of barbiturates in the plasma. This was done by a spectrophotometric method which is a modification by Broughton (1956) of the original method of Goldbaum (1952). The drug was identified as butobarbitone in a concentration in the plasma of 10.2 mg. per 100 ml. In spite of his fairly good general condition it was realized that he was in a dangerous state because, in this hospital, the previous highest recorded level of barbiturate in the blood, as butobarbitone, was 7.7 mg. per 100 ml. This was in the case of a young man who remained unconscious for 90 hours, in the first 72 hours of which he had been in deep coma. He passed no urine for 40 hours, his chest had given rise to some anxiety, and he had to be submitted to bronchoscopic aspiration. On regaining consciousness, his blood level of barbiturate was 2.5 mg. of butobarbitone per 100 ml. (Broughton *et al.*, 1956; Case 20).

The passage of the tube for gastric aspiration was followed by a fall of blood-pressure to 70/50 mm. Hg, but the pulse remained at 90. The blood-pressure then gradually rose again to about 88/55 mm. Hg. At 1.15 p.m. his breathing was slower and more shallow; this was accompanied by slight cyanosis and rise of pulse rate to 120 and blood-pressure to 140/100. By means of an Oxford inflator he was given oxygen through a face-mask for a couple of minutes, after which time the breathing was more natural and the blood-pressure fell to a steady level of 100/70 mm. Hg. At 2.30 p.m. a length of fine "polythene" tubing was passed through the nose into the stomach for feeding purposes. This was followed by a progressive worsening of his condition. The blood-pressure fell and his breathing almost stopped. The lungs were intermittently inflated with oxygen for a few minutes, after which he was able to breathe spontaneously for a short period, the blood-pressure rising to about 70/50 mm. Hg. However, this state of affairs would last for only five minutes or so, then again respiration would become inadequate and the blood-pressure would fall.

At about 3.30 p.m. spontaneous respiration ceased and did not return; he was pulseless, with an unrecordable blood-pressure. Thereafter, oxygen was given at about 12 inflations a minute, using an Oxford inflator, and no attempt was made to discontinue this treatment. The pulse became just perceptible with a blood-pressure of 50/40 mm. Hg. A cuffed endotracheal tube was then passed through the mouth and the lungs were inflated. An intravenous infusion of L-noradrenaline in 5% glucose solution was given and the rate of infusion adjusted to maintain a systolic blood-pressure of between 110 and 140 mm. Hg. A tracheostomy was performed and a short cuffed endotracheal tube passed. This was connected to a Radcliffe positive-negative-pressure respiration pump, which was set to work at 14 inflations a minute and adjusted to give a volume of respired air of about 8 litres a minute.

Thus far, at 5 p.m., the man was still alive, with his respiration and circulation being artificially maintained. It was clear that this regime would probably be required for a long time, possibly six or seven days. An adequate unassisted circulation and respiration were unlikely to return until the blood level of barbiturate, which was now 12.4 mg. of butobarbitone per 100 ml., had fallen substantially. The only natural method of elimination of the drug would be by detoxication in the liver and excretion by the kidneys, and this was likely to be slow, as it was in the case previously mentioned. It was thought, therefore, that an attempt should be made to dialyse some of the barbiturate from the blood, for, if this was successful, it might be life-saving or at least would reduce substantially the period of coma, with its attendant risks. No appreciable effect, apart from transient convulsive twitching, had been attained with a total of 500 mg. of bemegride given intravenously at the rate of 100 mg. every five minutes.

Consequently, contact was made with the Renal Unit at Princess Mary's Royal Air Force Hospital, Halton, who agreed to the transfer of the patient for haemodialysis. However, it was thought to be a prohibitive risk to move the patient by road because of the precarious state of his circulation. At 9 p.m. the decision was made to transport the artificial kidney to the patient, a distance of some 30 miles (48 km.). This was possible as no immediate dialysis was contemplated on any of the patients already in the renal unit. At 10.30 p.m. a team of four with the Kolff twin-coil artificial kidney and equipment (see Fig. 1) left Halton, and two and three-quarter hours later, at

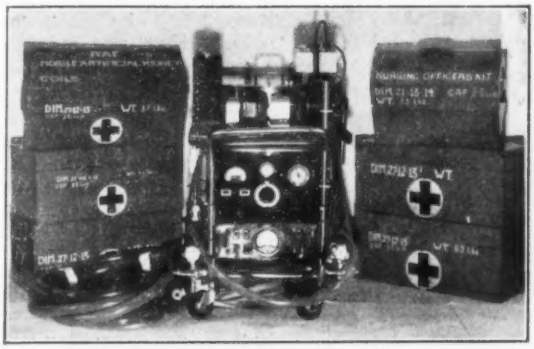

FIG. 1.—Kolff twin-coil artificial kidney with the equipment required for transport. Total weight 600 lb. (272 kg.). Team employed, four persons.

1.10 a.m. on September 11 dialysis was started. As the patient was not in renal failure it was decided to give intravenously 1.5 litres of fluid during dialysis, in order to maintain a reasonable urinary output. We were unable to weigh the patient, but from experience it was estimated that this amount of fluid would be lost owing to ultra-filtration.

During the seven hours of haemodialysis the patient's blood-pressure was maintained at about 130/100 mm. Hg. by varying the rate of infusion of L-noradrenaline.

At 4.45 a.m., after three and a half hours' dialysis, both pupils reacted to light, albeit sluggishly: painful stimulation by a strong pinch would evoke a slight movement of the limb and a temporary abortive attempt to fight against the rhythm of the mechanical respiratory pump.

At 5.30 a.m. he could breathe unaided for a short period, with a tidal air volume of between 350 and 400 ml.

At 8.10 a.m. dialysis was stopped because, during the preceding hour and a half, his peripheral circulation was not as good as it had been and a faster infusion rate of L-noradrenaline was being required to maintain the blood-pressure. At this time his temperature was 102.2° F. (39° C.), having been 96° F. (35.6° C.) at the beginning of dialysis. The state of the pupils and his response to painful stimuli were much as they had been halfway through the dialysis, though his responses varied. At the end of the period of haemodialysis the level of butobarbitone in the blood had fallen to 7 mg. per 100 ml. The dialysing bath fluid had been changed twice, at the second and fourth hours. In all, 1.51 g. of butobarbitone was recovered from the bath (Fig. 2). Dialysis was continued for seven hours, and by 10.30 a.m. the team with the kidney and equipment were back at Halton—12 hours after departure.

In the course of the next few hours the patient's condition steadily improved; the pupillary responses were brisker, he reacted to pain and made spontaneous swallowing movements. Unaided respiration was possible, though this was inadequate, and when mechanical breathing was started again this provoked a cough. At 6.30 p.m. the pupils reacted consensually and a flexor plantar response could be obtained.

During that night he began a brisk diuresis. At 10 a.m. on September 12 both knee-jerks were present and he reacted to painful stimuli; voluntary respiration was possible, but it was thought to be still inadequate. That same evening he moved his arms and head from side to side, making vigorous swallowing movements during a trial period of spontaneous respiration, and he had a good cough reflex. Throughout that day the rate of infusion of L-noradrenaline had been reduced progressively without causing any fall in blood-pressure. It was discontinued eventually at 3.45 a.m. on September 13.

At 9.30 a.m. on September 13 the blood-pressure was 130/90 mm. Hg. No L-noradrenaline had been given for nearly six hours. He could breathe unaided at the rate of 36 breaths a minute, with a respiratory volume of 7.3 litres a minute. He moved all four limbs voluntarily and reacted quite briskly to painful stimuli. During the morning he responded to his name by opening his eyes. At 1 p.m. the mechanical respiratory pump was stopped finally and breathing thereafter was spontaneous. At 6 p.m. he could obey simple commands, and at midnight would utter a few syllables when spoken to.

The following morning, September 14, he was wide awake and talking and complaining of discomfort in the left arm where the arterial and venous catheters had been inserted. The tracheostomy tube was removed and also the indwelling urethral catheter. He took a light lunch unaided. Thereafter his progress was uneventful and he made a complete recovery apart from an anaemia—haemoglobin 70% (10.5 g./100 ml.). He was discharged from hospital on September 25, 15 days after admission. His progress is illustrated in Fig. 2, where it is shown that consciousness returned when the level of butobarbitone in the blood was 2.5 mg. per 100 ml. The amounts of barbiturate recovered from the urine and the dialysing bath are also recorded.

On recovery he had no recollection of having taken any sleeping tablets; he was cheerful and not in any way depressed. He remembered being disappointed that he had not slept very well for three or four nights before his admission to hospital and remembered where his wife had kept her box of butobarbitone tablets. Therefore we were forced to conclude that he had taken this massive dose of barbiturates accidentally; probably he took one or two tablets at first and later, in a drowsy state, took the remainder unknowingly.

Since discharge from hospital he has been seen in the out-patients department. He is back at his original occupation, well in health and in good spirits. He seems to be none the worse for his near-fatal adventure. Examination and testing by a clinical psychologist failed to demonstrate any recent intellectual deterioration such as might have occurred as the result of cerebral hypoxia or hypotension.

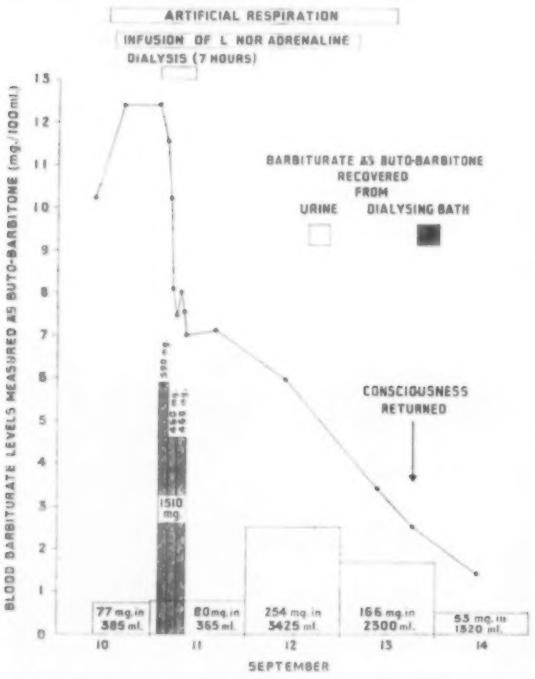

FIG. 2.—Day-to-day progress showing blood-barbiturate levels measured as butobarbitone and also the amounts of butobarbitone recovered from the urine and dialysing bath of the artificial kidney.

Discussion

This case illustrates the essential points in the management of severe barbiturate poisoning. If necessary, respiratory ventilation of the lungs can be carried out by a mechanical pump through a short cuffed endotracheal tube and an adequate blood-pressure maintained with L-noradrenaline. There is no doubt that haemodialysis by the artificial kidney substantially reduced the duration of coma with all its attendant dangers. The amount of butobarbitone removed from the body by dialysis, 1.51 g. in seven hours, was much greater than the amount eliminated in the urine, 0.63 g. in 7,795 ml. of urine passed in four and a half days. Not all barbiturates react to dialysis in the same way: phenobarbitone can be readily removed by dialysis, amylobarbitone is slightly dialysable, and so to a lesser extent is pentobarbitone, but secobarbitone is almost

undialysable (Sunshine and Leonards, 1954; Kolff, 1954). These differences are due to the variation in the binding of the barbiturate molecule to blood proteins. No reference could be found concerning the susceptibility of butobarbitone to dialysis, but from the experience in this case it would appear to behave in a similar fashion to amylobarbitone.

We consider that the artificial kidney will be required only in exceedingly severe cases of barbiturate poisoning not in renal failure. However, in the occasional case in which renal failure develops its employment will almost certainly be essential. It has been shown that the Kolff twin-coil artificial kidney is easily transportable, but only on rare occasions could this movement be contemplated. In general the majority of patients can be brought to the artificial kidney, which should not be moved from its parent hospital, apart from a second apparatus being available, unless (*a*) no patient in the unit requires dialysis, and (*b*) the distance involved is short—that is, not more than, say, 50 miles (80 km.).

This is the first time in this country that an artificial kidney has been moved to another hospital to treat a patient.

Summary

A case of severe but probably accidental poisoning by butobarbitone is described in which mechanical artificial respiration and an infusion of L-noradrenaline were employed when spontaneous respiration failed and the blood-pressure fell profoundly. The duration of coma was substantially reduced by using a Kolff twin-coil artificial kidney to dialyse butobarbitone from the blood, 1.51 g. being extracted in seven hours, compared with 0.63 g. from the urine in four and a half days. The artificial kidney was transported 30 miles (48 km.) by road to the patient, who made a complete recovery.

We thank Dr. A. M. Cooke, under whose care the patient was admitted, for his advice and encouragement to publish; the Director-General, Medical Services, Royal Air Force, for permission to publish the Service details; and Mr. G. Higgins, assistant biochemist to the United Oxford Hospitals, who carried out the numerous estimations of barbiturate and without whose help it would have been impossible to present this report. We gratefully acknowledge the help given by Mr. W. S. Lund, Mr. K. Cronin, Dr. A. Crampton Smith, and the members of the team from the R.A.F. Renal Unit—Squadron Officer M. Heyward, Flight Lieutenant N. V. D. Bunker, and Pilot Officer J. E. Scott.

REFERENCES

Alwall, N., Lindgren, P., and Lunderquist, A. (1952). *Acta med. scand.*, **143**, 299.
Broughton, P. M. G. (1956). *Biochem. J.*, **63**, 207.
—— Higgins, G., and O'Brien, J. R. P. (1956). *Lancet*, **1**, 180.
Eckenhoff, J. E., and Dam, W. (1956). *Amer. J. Med.*, **20**, 912.
Goldbaum, L. R. (1952). *Analyt. Chem.*, **24**, 1604.
Kolff, W. J. (1954). *A.M.A. Arch. intern. Med.*, **94**, 142.
Koppanyi, T., and Richards, R. K. (1958). *Curr. Res. Anesth.*, **37**, 182.
Locket, S., and Angus, J. (1952). *Lancet*, **1**, 580.
Nilsson, E. (1951). *Acta med. scand.*, **139**, Suppl. 253.
Shulman, A., Shaw, F. H., Cass, N. M., and Whyte, H. M. (1955) *Brit. med. J.*, **1**, 1238.
Sunshine, I., and Leonards, J. R. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **86**, 638.
Walsh, W. P., Kyle, L. H., Doolan, P. D., and Jeghers, H. J. (1952). *Amer. J. Med.*, **13**, 104.

Pakistani citizens living in Glasgow have presented three mobile dispensaries to the Pakistan Government. This is in response to an appeal by Pakistan's Minister of Health, who visited Glasgow recently (*Pakistan News*, September 15).

C

GRISEOFULVIN IN TREATMENT OF INFECTIONS OF SCALP DUE TO MICROSPORUM CANIS

BY

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Griseofulvin is an antifungal antibiotic isolated originally from *Penicillium griseofulvum* by Oxford, Raistrick, and Simonart (1939). Investigations on its ability to control pathogenic fungi were initially in the field of plant pathology. Some success was obtained, and a product containing griseofulvin as the active principle has been marketed for the control of a disease of glasshouse crops. Its possible application in human and veterinary mycology was demonstrated by Gentles (1958), who studied its effect on ringworm infection in guinea-pigs. Subsequently, Lauder and O'Sullivan (1958) used it successfully in calves infected with *Trichophyton verrucosum*. The use of the drug in human infections was first reported by Williams, Marten, and Sarkany (1958). Since November, 1958, Messrs. Glaxo have generously made available supplies of the drug to various centres in the United Kingdom and elsewhere, and already the American workers Blank and Roth (1959) have recorded preliminary results in the treatment of 31 cases of various kinds of ringworm.

Present Series

In this paper the results of griseofulvin treatment of 19 cases of *Microsporum canis* infection and observations of side-effects (or rather their absence) in a total of 50 children with various kinds of ringworm are discussed.

Infections of the scalp hair by *M. canis* offer certain advantages over other fungus diseases in any trial of griseofulvin, since the effect of the drug can be readily observed by the behaviour of fluorescence of infected hairs under Wood's light. Most dermatologists agree that this type of infection does not require *x*-ray epilation, yet is hardly, if at all, influenced by topical treatment. Spontaneous cure takes place in most cases in about three months. Little is lost in practice by treating these children with a new, untried, but apparently safe oral fungicide. Cases of *M. audouini* infection have not been seen in Belfast for several years and consequently none was available for treatment.

Treatment.—The 19 patients with *M. canis* varied in age from 15 months to 12 years and all were given griseofulvin in a dosage of 0.25 g. three times daily. The duration of treatment varied from 3½ to 10 weeks (average 6 weeks), as we do not yet know the optimum duration of treatment. The results are summarized in Table I.

Clinical Appearance

There was nothing dramatic about the changes in the clinical appearances of the 19 cases, all but one of which had symptomless non-inflammatory patches. This contrasts with the striking improvement seen in cases of infection of the non-hairy skin by various dermatophytes, and also noted in our cases not included in this trial, and recorded by Williams *et al.* (1958) and

TABLE I.—*Results of Griseofulvin Treatment of* 19 *Patients with M. canis Infection of Scalp*

Case No.	Age (Years)	Duration before Treatment (Weeks)	Weeks after Starting Treatment		Duration of Treatment (Weeks)	Remarks
			W.L. Neg.	Cult. Neg.		
1	3	3	3	After 4	7½	Nausea on one occasion (?)
2	7	Several	3	11	5	One neg. culture at 5 weeks
3	4	2-3	6½	8½	7	
4	7	12	4	15	3½	Two neg. cultures at 9 and 11 weeks
5	5	4	9	After 12	11 (one week omitted)	Case discussed in detail
6	8	½	3½	10½	3½	
7	5	2	7½	10½	8½	
8	12	1	3	8	3½	
9	4	1	2 (fluores. seen on later occasions)	After 12	7	Griseofulvin stopped because of nausea
10	2	1	3	After 3	4	
11	2	1	After 3	,, 3	4	
12	9	3	1	,, 3	4	
13	11	2	2	,, 3	4	Inflammatory (moderately)
14	12	1	After 1 (between 1-2½)	5½	4½	
15	8	1	4½	12½	8½	
16	6	½	5½	12½	7½	
17	3	3	4	15 single neg. at 11	7	
18	4	1	3½	16½	10	
19	5	1	6	After 10	8	

Blank and Roth (1959). Some objective improvement was usually apparent in about four to six weeks of treatment, but some abnormality such as erythema and partial baldness was usually present up to 10 to 14 weeks after treatment began. One single inflammatory infection did not differ in its behaviour from the non-inflammatory infections.

Examination by Wood's Light

It was noted that within a period of a few weeks, usually about three, the affected area became *completely* non-fluorescent, which is in agreement with the observations of Williams *et al.* (1958) on a single patient with *M. audouini* infection of the scalp. This dramatic change differs in certain respects from that which Gentles (1958) observed in *M. canis* infections in guinea-pigs treated with griseofulvin. He states: "It was noted that under Wood's light the infected hairs of treated animals fluoresced only at the tips." It was expected that this might also happen in the children whom we treated, but in only one of the 19, described in detail below, was there any evidence of fluorescence at the tips of the hairs. Initially infected hairs were brilliantly green under Wood's light; one to three weeks later they were beginning to dull, and then apparently quite suddenly the affected areas became completely non-fluorescent.

The most likely explanation of the difference between the children and the guinea-pigs would appear to be that the animal hair is more robust. It would tend to break somewhat later, since it could withstand hyphal invasion by the zoophilic fungus *M. canis* better than the average child's hair. As hair destruction is reduced by griseofulvin a small fluorescent tip might well be expected to be seen in the animal but only occasionally in the child. Our observations indicate that in children with *M. canis* infection the changeover from infected to normal hair is very abrupt. On the other hand, the anthrophilic fungus *M. audouini* might be expected to show fluorescent tips under griseofulvin treatment.

Mycological Culture

As the trial continued it was disappointing to find that the routine laboratory cultures taken from hair samples, scales, and debris from the area continued to be strongly positive. In Case 18 (Table II) this continued for at least 14½ weeks after treatment was started, though during this period a negative culture was found on one other occasion. In contrast, under Wood's light the infected areas were non-fluorescent 17 days after treatment began. In this particular case griseofulvin was continued for 10½ weeks—the longest in the series.

Table I gives the details of the results in the other cases. Four gave negative cultures after 3 weeks, one after 4 weeks, and one after 5½ weeks, but all the others were still positive up to at least 8 weeks from the date when treatment was started.

From these observations it is obviously important to have more than a single negative culture before deciding that a child has become free of the infection. We think that at least three consecutive negative cultures and microscopical examinations of carefully selected material (hairs, debris, etc.) should be taken at weekly (or longer) intervals before it can be concluded that an individual is free from infection. In a number of our patients the follow-up with repeatedly negative cultures was continued up to 16 weeks after the appearance of the first negative result.

Such strict criteria of cure as we have used had not been employed in many centres (and certainly not in ours) before this griseofulvin trial, and we are unaware of any detailed reports of the follow-up of patients with scalp infection by *M. canis* which cleared spontaneously or with local treatment. In the interpretation of the results of other treatments it must always be borne in mind that contamination of the culture inoculum by a local fungicide would prevent growth of the fungus. Only too often when a child has become negative to Wood's light it has been accepted that the individual was free from infection.

Mycological Results

An explanation of the effect of griseofulvin on hairs invaded by *M. canis* can be obtained from the detailed examination of one unusual patient (Case 5).

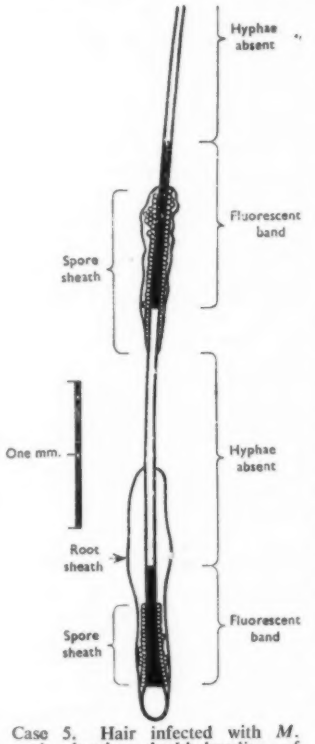
Case Report

This child was unique in several fortunate ways. In the first place, he had one week's treatment, followed, owing

TABLE II.—*Course of Infection in Case* 18

Weeks:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Attendances	++	+	+	+		+	+	+	+		+		+		+		+	+		+		+
Griseofulvin	xxxx

to an oversight, by one week without treatment; then treatment was started again and regular examinations were continued. Secondly, the hyphal invasion of this boy's hair was insufficient (either because of the minimal invasion by the fungus or because of the unusual robustness of the boy's hairs) to cause infected hairs to break. The result is that we obtained long hairs for mycological examination, many of which showed in continuity bands of fungus invasion and bands of fluorescence illustrating the effect of the drug. Infected hairs examined after his first visit showed no unusual clinical, cultural, or microscopical characters. There was a well-developed ectothrix spore sheath surrounding the basal portion of the hair, consisting of a closely packed mass of polygonal arthrospores. These were normally isodiametric, and varied from 1.2 to 3.6 μ (mostly from 2.4 to 3 μ) in diameter. *M. canis* was obtained in culture, and this differed in no respect from other isolates of this species. The rate of growth and pigment production, the appearance of the developing colony, and microscopical characters were typical of *M. canis* on the media used in its isolation and maintenance. Numerous fusiform, multiseptate, rough-walled macroconidia, varying from 54 to 94 μ in length, were produced and appeared approximately three to four days after the hairs had been sown on the agar surface.



Case 5. Hair infected with *M. canis* showing double-banding of fluorescence.

Little change was seen a week after treatment had begun, but one interesting feature was demonstrated microscopically—namely, non-fluorescence of an infected hair. This particular hair was a little over 2 mm. in length and lay for the most part within an epidermal scale and the closely packed cylindrical cells of the outer root sheath. The hair cuticle had been destroyed. The ectothrix spore sheath was well formed and no morphological abnormalities were noted. The possibility that fluorescence was present but had been masked by the overlying scale cannot be altogether dismissed, but is considered unlikely. Other hairs were noted where fluorescence was intense and could be seen through the overlying scale. In later specimens well-formed sheaths with no overlying scales were found, and in these fluorescence was entirely absent.

On the child's third visit the discovery was made that one week's treatment had been omitted, and the effects of this were noted in material examined the following week. In this hair (see Diagram) there were two obvious bands of fluorescence, the lower 0.1–0.9 mm. from the bulb, and the upper 2.6–4 mm. from the bulb. There is no trace of hyphal continuity between these two regions, showing that the lower (basal) infection must have been caused by reinfection, presumably from hyphae within skin debris. Reinfection had been made possible, presumably as a result of interruption in treatment. This double-banding was noted in three other hairs which were collected on this occasion, though in one of these the reinfection was not accompanied by production of fluorescence.

After seven weeks' treatment hairs examined microscopically showed that, though the hair itself was free from infection, normal hyphae could be detected in the overlying scale. The fungus was therefore still present and still presumably capable of bringing about reinfection. The following week a number of hairs showed a basal infection, with a well-formed and apparently normal spore sheath. Fluorescence was inconspicuous and confined to a narrow zone at the distal end of the infection. All but one of the hairs showed a second distal infection which was non-fluorescent. This finding was quite unexpected, and suggested that treatment had been allowed to lapse 7 to 14 days previously, allowing re-entry and re-establishment of the fungus within the hair. It is perhaps a cause for some concern that treatment over a period of eight weeks produced no significant microscopical changes from the material examined at the outset.

That griseofulvin is effective against the fungus was borne out by microscopical examination of an infected hair. The change from infected to healthy hair material was often very abrupt and there was no transitional zone. Fungal hyphae abutting on to the "protected" keratin showed marked morphological abnormalities—gross distortions, malformations, and swellings could be seen up to 12 μ in diameter. It seems clear that if treatment is continuous the newly formed hair is impervious to invasion by the ringworm fungus. When treatment is interrupted, or perhaps inadequate, colonization of the hair can be expected from viable fragments of fungal material contained in superficial debris, or perhaps from a residual intrafollicular reservoir. In a number of instances, however, hyphae could be detected in portions of hair that were presumed to be protected by griseofulvin. This poses the problem of adaptive resistance, differential absorption of griseofulvin, and variation in the physical properties of the different hair strands, which are outside the scope of this communication.

It seems evident that hairs react in a different manner, and a number of anomalies have been noted—for example, failure to establish an impenetrable griseofulvin barrier. If individual hairs differ in their rates of growth and their robustness, it is perhaps not surprising that an examination of a number of hairs will show different degrees of tolerance to a pathogenic fungus. It is possible that the concentration of griseofulvin incorporated in a growing hair will be dependent on a variety of factors, including amongst others the relative rate of growth of the hair, and it may be that in slowly growing hair less griseofulvin will be found than in a faster-growing one.

Toxic Effects

One of the most remarkable properties of the drug to date has been its low toxicity. The effect on mitosis, reported by Paget and Walpole (1958), when the drug is given intraperitoneally or intravenously in very large doses to experimental animals, has not been seen when the drug has been given orally in larger doses and for longer periods than are necessary for clinical purposes. Barlow (personal communication) has demonstrated a possible effect of the drug on the white-cell count of patients and urges caution at this early stage in clinical trials, but it is reported by Sulzberger and Baer (1959) that "Harvey Blank, who examined all of his patients carefully in many directions during the course of treatment, reported normal values with respect to body weight; fasting blood sugar; blood urea nitrogen;

alkaline phosphatase; thymol turbidity tests; measurements of the electrolytes in the blood, complete blood counts; urinalyses; and sternal bone marrow examinations."

At each visit all children and their parents were carefully questioned about any symptoms which might have been attributed to the griseofulvin. In only 2 out of 50 children were any complaints recorded. Both these children had an *M. canis* infection and are included in our 19 cases; both had nausea; in one it was insufficient to merit discontinuing treatment and passed off within a day or two, so that it is doubtful if this was due to griseofulvin, but in the other the mother felt that the nausea was being caused by griseofulvin and she herself stopped treatment, but this was after a period of seven weeks. We cannot say for certain that the nausea recorded in these two children can be attributed to the drug. Though we had no control group to compare with our treated group with regard to toxic symptoms, a number of minor illnesses in a group of 50 children during an observation period of several months would be expected.

Routine blood examinations were not carried out in our series during the course of treatment, because had we done this it is most unlikely that the children would have re-attended.

Conclusion

It seems obvious that the continually positive cultures which were obtained from our patients must be due to debris in and around the hair and particularly to *intrafollicular* debris. The presence of a reservoir of infection in discrete skin scales has, in fact, often been observed in our material. This is going to prove a very difficult stumbling-block in the practical management of ringworm infections of the scalp. None of our patients received any form of local application; indeed, because this was a clinical trial in which we were determining first of all the effect of griseofulvin alone, the children were told not to wash their hair or to scrub the affected area. About halfway through the trial, when it became apparent that oral griseofulvin therapy alone failed to eradicate infection satisfactorily, mothers were told to scrub and wash the child's scalp twice a day after the initial three to four days' treatment. It is thought that this should not be done until the child has had a few days' treatment with griseofulvin, otherwise infection of new areas may take place, but once the drug has been incorporated in the hairshaft and keratin it would seem that a determined effort to get rid of all the debris which carries infection should be made. The application of a strong fungicide and shaving of the affected areas at regular intervals are two other possibilities at present being tried out during treatment with oral griseofulvin, but results to date have been disappointing.

A most important point to record is that none of the cases, either in this trial or with other kinds of fungus infection not included in this series but treated to date, have developed fresh lesions during treatment with griseofulvin. This suggests that the drug may be of the greatest possible value in protecting contacts in the home or in residential schools.

Summary

In our experience griseofulvin is non-toxic to children in a dose of 0.25 g. three times daily for periods of up to 10 weeks.

Fungal invasion of hair is stopped abruptly soon after the drug is given, and new areas of infection do not appear. Debris, probably intrafollicular, remains infected and the organism can be recovered readily for long periods (up to 14 weeks) after treatment has started.

Wood's-light fluorescence usually disappears in one to six weeks (average three weeks). With *M. canis* infections fluorescent tips are only exceptionally found.

In one rather unusual case in the series fluorescence was observed eight weeks after treatment had started; after the second week this fluorescence appeared at various distances from the surface of the scalp; positive cultures were obtained up to 12 weeks after the initiation of treatment, and microscopical examination often revealed a well-established infection in a non-fluorescent portion of hair.

Future studies should be directed towards a method for the removal of infected debris. Such methods might include washing, scrubbing, and/or shaving the affected areas, and the application of local fungicides. It is already apparent that, though griseofulvin is a most remarkable advance in antibiotic therapy, it is insufficient in itself to cure scalp ringworm (at least that due to *M. canis*) within a reasonably short period.

We thank Dr. J. C. Gentles and Dr. Jacqueline Walker for helpful discussion concerning the mycological interpretation of our material, and Dr. Ivan H. McCaw and Professor George Dick for their active interest in the trial. Mr. J. C. H. Hanson, of Glaxo Laboratories, provided us with much unpublished data concerning griseofulvin. Glaxo Laboratories generously provided all the griseofulvin ("grisovin") used in this trial. Photographs for record purposes were taken by Mr. R. G. Woods, and the diagram was prepared by Mr. George Smith.

References

Blank, H., and Roth, F. J. (1959). *A.M.A. Arch. Derm. Syph.*, **79**, 259.
Gentles, J. C. (1958). *Nature (Lond.)*, **182**, 476.
Lauder, I. M., and O'Sullivan, J. G. (1958). *Vet. Rec.*, **70**, 949.
Oxford, A. E., Raistrick, H., and Simonart, P. (1939). *Biochem. J.*, **33**, 240.
Paget, G. E., and Walpole, A. L. (1958). *Nature (Lond.)*, **182**, 1320.
Sulzberger, M. B., and Baer, R. L. (1959). *Excerpta med. (Amst.), Sect. XIII*, **13**, 145.
Williams, D. I., Marten, R. H., and Sarkany, I. (1958). *Lancet*, **2**, 1212.

"Human remains which are unearthed in the course of excavation are with the sanction of the Home Office, the Ecclesiastical Authorities, the City Coroner, and the City Police reverently re-interred in an approved burial ground or cremated at an established crematorium. During the year all human remains were removed from the crypt of the St. Swithun London Stone Church in Cannon Street and taken to a cemetery in Surrey where they were re-interred. The crypt has been closed for burial since 1853. The majority of the remains were in lead coffins most of which were identifiable, the names on the coffins still being legible. During excavation work on a building site bounded by Farringdon Street, Stonecutter Street, and Shoe Lane some human remains were discovered. The bones were of great age, and Mr. N. C. Cook, B.A., F.S.A., the Keeper of the Guildhall Museum, considered that the bodies were probably buried prior to the Great Fire of London. The absence of coffins suggested that the site had been a plague pit in 1665. The British Museum became interested in these relics, and as a result of their request the Home Office gave permission for some of the bones to be retained in the British Museum (Natural History). The rest of the remains were cremated at the City of London Crematorium at Little Ilford." (*Report of the Medical Officer of Health for the City of London for the Year 1958*, p. 16.)

GRISEOFULVIN IN TREATMENT OF PERSISTENT FUNGAL INFECTIONS OF THE SKIN

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The recent discovery that griseofulvin can be used orally as a fungistatic, effective against the dermatophytes, represents a major advance in therapy. In this country the majority of cases of ringworm are due to infection of the feet by organisms which can be controlled by topical fungicides, albeit with a high relapse rate. In recent years, however, there has been an increased incidence of infection by *Trichophyton rubrum*, a species which gives rise to resistant and intractable infections, especially when the nails are infected, and there would appear to be a small group of people in whom infection of multiple nails by this organism has hitherto been incurable. The preliminary papers of Williams, Marten, and Sarkany (1958) and Blank and Roth (1959) have shown that this organism, like the other dermatophytes, is inhibited *in vivo* by griseofulvin, and there would appear to be every likelihood that these infections may soon be controllable..

Clinical experience of the drug is as yet too limited for a great deal to be known about the effective dosage, the duration of treatment required, the long-term results, and the possibility of toxic reactions.

The following report records the experience of two independent groups of observers who have handled the drug during the last seven months. Of the 34 patients treated, 26 have had long-standing infection of multiple nails and skin by *T. rubrum*, previously resistant to numerous lines of treatment, including surgical avulsion of nails.

In each case fungus has been demonstrated microscopically in the affected site and identified by culture prior to starting treatment. All patients have been examined and scrapings checked at regular intervals, and in 12 instances blood counts have been done daily for 14 days and thereafter at weekly intervals. In the following report an area is said to have cleared only when the clinical state has returned to normal and fungus can no longer be demonstrated microscopically or by culture; in most instances photographs have been taken to compare changes in nail infection; except in the group specified, no local treatment has been carried out.

Clinical Cases and Results

Two children with candidiasis and one man with tinea versicolor showed no clinical change as a result of treatment.

Two men showing typical cattle ringworm due to *Trichophyton verrucosum* each developed an Id reaction two days after starting treatment (2 g. daily). This settled when griseofulvin was stopped after seven days, and the primary lesions resolved over a period of three weeks. It was not felt that the duration of infection had been significantly modified.

One man showing a vesicular infection of the instep due to *Trichophyton mentagrophytes* var. *interdigitale* was given 2 g. daily for two weeks followed by 1 g. daily for two weeks. There was immediate symptomatic improvement, but scaling persisted for five weeks and viable fungus was present in the sole for six weeks. Re-examination at regular intervals during the next three months showed the soles to be clinically normal, there being no evidence of fungus microscopically.

Infection by T. rubrum

(*a*) *Infection of Smooth Skin Only.*—Two patients, each showing typical scaling patches on the legs, were given 2 g. daily for two weeks followed by 1 g. daily for one week. Each showed subjective improvement within a few days and in one patient scrapings became negative after 10 days and have remained so over a period of six months. In the other patient, scrapings still remained positive after three weeks, and this case is still under observation.

(*b*) *Intractable Infection of Multiple Nails and Adjacent Palms, Soles, or Smooth Skin.*—In this group 26 patients have been treated, all of whom have had chronic infection by *T. rubrum*, in most cases of many years' duration. Nearly all patients experienced symptomatic relief as regards skin: itching disappeared from the smooth-skin lesions in two to three days, and scaling became less evident within a week, from the palms and soles in about four to six weeks. In view of the different factors, influencing infection of the smooth skin, palms, soles, fingernails, and toenails, infection in each of these sites is considered separately.

Variations in Dosage

(1) 2 g. daily for two weeks, followed by 1 g. daily for one week. Two patients, each showing infection of soles and multiple toenails, were not influenced by treatment, and fungus was still present in both sites six months after completing treatment.

(2) 2 g. daily for three weeks. In this group 11 patients were treated six months ago and have been observed at regular intervals since. Most of these patients experienced clinical improvement during the period of treatment, and in many cases this was maintained for a considerable time after treatment was stopped. In 10 patients the soles and toenails were affected. In two instances the soles cleared and have remained so for six months; in the other eight, though there was objective improvement, fungus has always been present. Occasionally toenails appeared to have improved clinically, but none has cleared. Five of these patients also had palmar and fingernail infection; in two patients the palms have cleared and have remained so, but in the other three, though there was clinical improvement, scrapings have remained positive. Growth of several fingernails has appeared to be nearer to normal, but infection has persisted in three patients. In one patient in whom infection was limited to the nail of the little finger, this nail has grown out normally, whilst, in another, two fingernails out of five infected nails have cleared. These nails cleared three to four months after the completion of treatment, and have remained clear.

(3) 2 g. daily for three weeks combined with the local application of benzoic acid compound ointment, B.P.C., to the affected site. This group, consisting of 10 patients, has also been observed for six months after treatment. All patients had infection of multiple toenails, and one patient was unable to complete treatment owing to toxic effects. While in no instances did toenails clear, in five patients they appeared to improve. Seven of these patients also had infection of the adjacent sole, and in two this has persisted, but cleared in the other five. Palmar infection was present in five patients, clearing in two but persisting in three. Several fingernails were infected in four patients and all showed clinical improvement. In one patient eight affected nails, in another one out of three, and in a third an infected right thumbnail have remained clear during the period of observation.

(4) 2 g. daily for two weeks followed by 1 g. daily for five weeks. One patient who had long-standing infection of all nails, palms, soles, and most of the smooth skin improved dramatically. The lesions of the smooth skin cleared in a fortnight and the palms and soles in six weeks. Several nails, both on feet and on hands, improved during and for three months after treatment, but fungus was still present in all nails five months after completing treatment. There has in the last two months been some relapse in the smooth skin, but both palms and soles remain clear. The second patient with infection of multiple toenails and fingernails, who was still on treatment at the time of writing, showed some clinical improvement in the nails, but fungus was still present.

(5) 2 g. daily for two months followed by 1 g. daily for 12 weeks. One patient showing infection of all toenails and soles experienced immediate symptomatic improvement, and scrapings from the soles became negative after five weeks, remaining so until the twelfth week of treatment, when a positive scraping was again obtained. There has been some clinical improvement of the nails, but fungus was still present in all of them. This patient is still under treatment.

Side-Reactions

Blood Counts.—These have been done in most cases at the same time of the day and by the same technician. In 4 out of 12 patients in whom regular blood counts have been done, considerable variation in the differential blood count was noted from day to day, but in no instance did the absolute count fall below 2,000. One patient who showed the most wide variation is referred to below.

General Reactions.—Several patients complained of headaches and some malaise, but in most cases not of sufficient degree to inconvenience them. Five patients developed erythematous rashes while on treatment; in one this cleared, though the treatment was continued, but in the others the reactions disappeared only when griseofulvin was stopped. In one of these the reaction occurred after completing three weeks of treatment, and this patient had an acute recurrence when she was given griseofulvin at a later date. Another patient who became febrile nine days after starting treatment complained of dizziness, general malaise, and fainting on two occasions, in addition to developing an extensive erythematous rash on the trunk. These symptoms settled as soon as griseofulvin was stopped. Four days later she was given a lower dosage—that is, 1 g. daily—and after five days again became febrile and vomited on several occasions. This again ceased when griseofulvin was stopped, but she had two further recurrences each time she was given the drug, in one instance when given in conjunction with antihistamines. Blood counts taken in relation to these episodes showed no significant blood changes.

Another patient developed severe headache, nausea, and dizziness within a few hours of taking the drug, and in the course of three days her absolute polymorph count fell from 8,200 to 2,200. Her symptoms cleared when treatment was discontinued but immediately recurred as soon as treatment was resumed, her count falling from 6,500 to 2,200 in 24 hours. During the next 10 days the count showed very wide variations between 5,000 and 2,000, never falling below the latter figure. Treatment had to be discontinued because of an increase in her symptoms. This patient was shown at the North of England Dermatological Society meeting in March, and after this, on the advice of Dr. J. F. Wilkinson, she was given the drug again as an in-patient. On this occasion she had no return of her symptoms or significant change in her blood count and she has now been on treatment for six weeks.

Discussion

The above results are in line with those of Williams *et al.* (1958) and Blank and Roth (1959). Griseofulvin is ineffective against infection by *Candida albicans* and *Malassezia furfur* but does influence infection by the other dermatophytes, including *T. rubrum*. In this series the periods of treatment varied from 3 to 14 weeks. There has been considerable variation in results, but in most cases lesions of the smooth skin have cleared in 10 to 14 days and palm and sole infection in 35 to 42 days. In no instance have toenails grown out normally, though many have shown clinical improvement. In several patients fingernail infection has responded and nails have grown out normally after periods of treatment of only three weeks.

It is difficult to draw conclusions from a small series, but it would appear that the results have been better in the group in which a topical fungicide was used concurrently. For example, in four patients showing between them infection of 21 fingernails, 10 nails regrew normally. This compares with an equivalent group in which there was no topical treatment: 5 patients had a total of 17 infected fingernails, of which 3 grew out normally.

Considerable variations in response to treatment are apparent, since courses of treatment lasting only three weeks have cleared fingernail infection in some instances, while periods of treatment of 7 to 14 weeks have failed to cure infection in other patients. A number of factors can account for such discrepancies, including variation in ability to absorb griseofulvin or to accumulate it in an active form at the site of fungal growth. Equally it seems possible that not only different species but also different strains of fungi may vary in their susceptibility to griseofulvin.

Since griseofulvin is fungistatic and not fungicidal, its mode of action would seem to be by inhibiting fungal growth in its mycelial stage, so that infection is carried away by the outward growth of keratins. In the smooth skin the inhibitory effect of griseofulvin will cause the fungus to lose its foothold in the normal process of desquamation of soft keratin. The exact

rate at which this occurs on the smooth skin of the trunk and limbs is uncertain, but, arguing from the above findings, it would appear that the infected layer is shed in approximately 10 to 14 days. Desquamation in palms and soles takes much longer, probably between four and six weeks.

Nail infection presents a different problem, since here keratin does not desquamate: hence it is necessary to wait for the nail to grow sufficiently for infection to be carried beyond the free edge. Rates of nail growth differ greatly, the fingernails growing approximately four times as fast as toenails (Le Gros Clark, 1958). An average rate of growth for the normal thumbnail is 3 mm. a month (Le Gros Clark and Buxton, 1938), so at least four months must be allowed for infection of fingernails to grow out, while well over a year would be required for infection to be eliminated from the nail of the big toe.

Whether it would therefore be necessary to administer griseofulvin continuously or intermittently over such a long period can be proved only by trial and error. Since the action is one of fungistasis, any temporary fall below the concentration necessary to inhibit fungal growth would allow reinvasion to take place, either from mycelium itself or from the germination of spores which are unaffected. This effect has already been observed in the hair root (J. M. Beare, 1959, personal communication), and it would seem reasonable to suppose that a similar effect could take place in the nail. Long-continued administration of the drug would in addition raise the question of resistance developing in the fungus. This has not yet been observed in the dermatophytes, but adaptation to fungicides has been observed among plant fungi (Parry and Wood, 1958).

Increasing use of griseofulvin will clarify the position about toxicity. In our series three patients were unable to tolerate the drug, but in spite of noting some variation in the differential blood count we have insufficient evidence to say that it has a toxic effect on the bone-marrow. Further patients, not included in this series, have also shown no significant haematological change. It would, however, appear important that this possibility is borne in mind, particularly in view of the report of Paget and Walpole (1958), who showed that it had a colchicine-like action on mitoses when given intravenously in large doses.

In our present state of knowledge it would seem that a combination of surgical removal of nails, with griseofulvin systemically and possibly the subsequent use of topical fungicides, would offer the patient suffering from chronic nail infection by *T. rubrum* the best chance of cure.

Summary

Thirty-four patients with fungal infections of the skin have been treated with oral griseofulvin in a dosage of 1–2 g. daily.

Two children with candidiasis and one man with tinea versicolor showed no improvement.

Two patients infected with *T. verrucosum* derived no significant benefit.

Infection by *T. mentagrophytes* in one patient cleared after four weeks' treatment.

Two cases of *T. rubrum* infection of the smooth skin were treated for three weeks; one cleared completely and the other improved.

Twenty-six patients with long-standing *T. rubrum* infection with nail involvement were treated for periods of 3–20 weeks. The majority improved, but in only one instance was the infection eradicated.

Toxic reactions are recorded and possible reasons for the wide variations in clinical response discussed.

Some of these cases were under the clinical care of Professor J. T. Ingram, Dr. F. F. Hellier, and Dr. S. T. Anning, and we would like to thank them for their co-operation and advice. We also thank the staff of the pathological department at both hospitals, and Dr. J. F. Wilkinson for his advice on haematology, Dr. Jacqueline Walker for kindly co-operating in the mycology, and Messrs. Glaxo Limited for generous supplies of griseofulvin.

References

Blank, H., and Roth, F. J. (1959). *A.M.A. Arch. Derm.*, **79**, 259.

Le Gros Clark, W. E. (1958). *The Tissues of the Body*, 4th ed., p. 310. Clarendon Press, Oxford.

—— and Buxton, L. H. D. (1938). *Brit. J. Derm.*, **50**, 223.

Paget, G. E., and Walpole, A. L. (1958). *Nature (Lond.)*, **182**, 1320.

Parry, K. E., and Wood, R. K. S. (1958). *Ann. appl. Biol.*, **46**, 446.

Williams, D. I., Marten, R. H., and Sarkany, I. (1958). *Lancet*, **2**, 1212.

THE MUSCULAR LESION IN HYPERTHYROIDISM

BY

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The occurrence of muscular weakness in hyperthyroidism is well recognized, but it is difficult to state exactly the incidence of muscular involvement, since normal function is hardly possible to define and mild degrees of impairment are most common. Evidence of a muscular lesion can probably be demonstrated in most hyperthyroid patients, and in some it may be the most important part of the disease. Twenty-six cases of hyperthyroidism with a varying degree of muscular involvement are described (See Table). The first two patients were seen a year before the rest of the series, and are included as examples of the rare severe form of muscle lesion (Cases 1 and 2). The remaining 24 were those of some 40 unselected hyperthyroid patients in whom evidence of a muscle lesion was particularly looked for clinically, and in many cases electromyographically, and whose progress was then followed for between one and two years.

The Muscular Lesion

In three patients (Cases 1, 2, and 3) severe muscular weakness developed acutely over the course of a few days, each patient having been hyperthyroid for a few weeks. Two of these three (Cases 1 and 2) had aching in the muscles, and one (Case 2) also had paraesthesia in the legs. Two (Cases 2 and 3) had mental confusion combined with an appearance of apathy—not real, but imposed by the profound weakness; also, the facial muscles were weak and speech became faint and indistinct, and all the voluntary muscles of the trunk and limbs were involved. Swallowing and respiration remained adequate in these patients, but deaths have been reported in similar cases, probably from respiratory insufficiency. In Cases 1 and 2 the diagnosis of hyperthyroidism was not at first considered. Both these patients responded rapidly to antithyroid treatment when

it was begun some two months after the onset of the muscular symptoms. These patients resembled certain cases described either as thyrotoxic coma, as distinct from crisis, or as apathetic hyperthyroidism (Lahey, 1932). The condition is probably not very rare, but is not always obviously of thyroid origin and if undiagnosed may be fatal.

In most patients there was a less severe, more chronic muscle lesion accompanied by obvious signs of hyperthyroidism. Some patients (Cases 4–16) complained of muscular symptoms, and weakness and wasting were easily confirmed clinically. Others (Cases 17–26) had no very definite complaints suggesting a muscle lesion, but this was nearly always demonstrable clinically as well as electromyographically, and it improved after treatment of the hyperthyroidism.

The muscle lesion was assessed clinically by simple tests; precise quantitative testing was not undertaken, and allowance was made for variations in age and physique of the various patients. Patients were asked to step from the ground up on to a chair; even those not complaining of muscular weakness often found great difficulty in doing so unaided. Some with little or no dyspnoea were obliged to crawl upstairs. Nearly all were unable to maintain abduction of the arms against the examiner's downward pressure. Other muscle groups were tested similarly. The weakness was much more pronounced in the shoulder and pelvic girdles than in the distal or bulbar muscles. One patient presented with backache due to weakness of his back muscles which responded to thiouracil and twice recurred when the drug was withdrawn. Pain was exceptional, however. Testing the strength of grip by maintaining pressure through a sphygmomanometer bulb was an unsatisfactory indication of hyperthyroid muscular weakness; the use of the hand was seldom demonstrably affected.

Muscular wasting was generally in proportion to weakness, but in many of the less severely affected patients it was not obvious. Wasting was usually most apparent in the scapular muscles, particularly in the supraspinatus and the posterior part of the deltoid, sometimes in the glutei or the quadriceps. The triceps, the most satisfactory muscle for electromyographic testing, showed gross wasting less clearly. Wasting which extended peripherally to include the small muscles of the hand was occasionally seen (Cases 1 and 2), but only when there was gross wasting elsewhere. Some patients with quite mild hyperthyroidism, but with rather severe muscle involvement, had lost much weight (over 20% of their body weight), probably owing to loss of muscle rather than fat. The smooth firm skin usually preserved in thyrotoxicosis suggests that the subcutaneous fat may be largely intact; creatine studies suggest that functioning mass, if not actual mass, of muscle is reduced.

In most of the patients studied the tendon reflexes showed characteristic quick but weak muscle contraction and quick relaxation. Exceptions were found occasionally in very severely affected muscles where the tendon reflexes were diminished or absent. The muscles in hyperthyroidism show fatigability, which has led to confusion with myasthenia gravis. However, the fatigability in thyrotoxicosis is less pronounced, and there is not the characteristic increase in myasthenic weakness as the day goes on. The two conditions are also distinguished by the failure of hyperthyroid weakness to respond to anticholinesterase. Normal responses to edrophonium chloride and to curare were shown in six patients thus tested.

Electromyography was done before treatment in all but two patients in the series, and in most of them it was repeated at least once after treatment had taken effect. In the majority of hyperthyroid patients tested the electromyogram was abnormal in a characteristic way, termed the "myopathic pattern" (Bauwens, 1955). Action potentials on volition were of high frequency and low voltage, and there was no evidence of

Summary of Cases

Case No.	Age and Sex	Muscle Involvement Clinically	External Ophthalmoplegia	Weight Loss (% of Normal)	B.M.R.	Radio-iodine Test	Serum Creatine (mg./100 ml.)	Creatine Excretion (mg./24 Hours)	Creatinine Excretion (mg./24 Hours)	Myopathic Pattern in Electromyogram	Treatment	Assessment After Treatment: Muscle Involvement Clinically	Assessment After Treatment: Serum Creatine (mg./100 ml.)	Assessment After Treatment: Myopathic Pattern in Electromyogram
1	M 21	Ac.+++	–	15	+37		1·30	124	1,090		Iodine. Surgery	–	0·45	
2	M 19	Ac.+++	–	20		+	0·70			+	Thiouracil	–		–
3	M 52	Ac.+++	–	20			0·78			+	Iodine. Thiouracil. Surgery	–		±
4	M 18	++	+	25	+15	+	0·55			+	Thiouracil. Surgery	–	0·45	–
5	F 20	++	+	24	+51		0·61	110	770	+	Iodine. Thiouracil. Surgery	–		–
6	F 33	++	–	25		+	0·93			+	Iodine. Surgery	±	0·50	±
7	F 63	++	+	25	+45		1·30				Thiouracil	±	0·56	
8	F 27	++	+	15	+49	+	0·95			+	Iodine. Thiouracil. Surgery	–		–
9	F 24	++	–	25	+51	+	0·74			+	Iodine. Surgery	–		–
10	F 45	++	+	20	+51	+	0·70			+	Iodine. Thiouracil. Surgery	±	0·40	±
11	F 58	++	–	20		+	1·18	226	654	+	Radio-iodine	–	0·45	–
12	F 51	++	+	24	+40		0·70		900	+	,,	±		±
13	F 36	++	–	8		+	0·95	237	680	+	Thiouracil. Surgery	–	0·35	–
14	M 67	++	–	20		+	0·77	Nil	1,039	+	Radio-iodine			
15	M 46	++	–	25	+38	+	1·1	58		+	,,	±		+
16	M 47	++	+	15	+45		1·1			–	Thiouracil. Radio-iodine	+		
17	F 47	+	–	12	+33	+	0·80	71	684	+	Radio-iodine	±	0·40	–
18	M 47	±	+	6	+41		0·88	Nil		+	Iodine. Surgery	–	0·28	–
19	F 48	+	–	10		+	0·37			+	Thiouracil	–	0·20	–
20	F 41	±	–	10			0·71			+	Iodine. Thiouracil. Surgery	–	0·51	–
21	F 34	+	–	15			1·13	168	756	+	,, ,,	±	0·35	±
22	F 60	+	–	25		+	0·91			+	Radio-iodine	±	0·53	–
23	F 42	±	–	8	+40		0·93	319	1,084	+	Thiouracil	±		–
24	M 30	+	–	15	+41	+	0·73	Nil	1,410	+	Thyroidectomy			
25	F 45	+	+	20	+40	+	0·70			+	Iodine. Surgery	–		–
26	F 59	+	+	10	+20		0·70			+	,, ,,	±	0·53	±

denervation or myelopathy. These findings were most readily obtained from the triceps, and this muscle was generally used for testing. An abnormal electromyogram, improving after treatment, was obtained from several patients with only minimal symptoms of the muscular lesion; a normal electromyogram was obtained from one patient with muscular involvement which clinically seemed quite pronounced (Case 16).

Electromyography in four other patients, not included in this series, with clinically doubtful muscle involvement showed no abnormality. The electromyogram returned towards normal after antithyroid treatment. The rate of return and its completeness varied and were independent of the type of treatment. In some patients the electromyogram was normal within two weeks of starting treatment; in others it was still abnormal, though improved after three months. The abnormal electromyogram provided supporting evidence that a disorder of muscle function was often present, and the invariable improvement after treatment suggested that the disorder was due to hyperthyroidism. The electromyographic findings were not quantitative, nor were they specific for hyperthyroidism.

Other Features

The diagnosis of hyperthyroidism was evident in most of the patients. Cases 1 and 2 were unusual in that the muscular weakness was profound and the diagnosis was not apparent at first. All the patients had a resting pulse rate of over 100, two had atrial fibrillation, several had mild heart failure—in Case 3 severe. Tremor, nervousness, irritability, and increased sweating were present, and either the B.M.R. or a radio-iodine test confirmed the diagnosis in most instances. Very high basal metabolic rates were not encountered, and some of the patients with much muscular involvement had only a moderate increase; sometimes other hyperthyroid symptoms appear mild, or perhaps are masked by weakness. Evidence of disordered creatine metabolism was found in most of the patients. The serum creatine was 0.7 mg./100 ml. or over in 22 out of 25 patients, and it invariably fell after treatment. The 24-hour excretion of creatine and creatinine was estimated in 11 patients: in 6 creatine excretion was excessive, in 5 creatinine excretion was probably subnormal. No other significant biochemical abnormalities were noted. The serum potassium was normal in those patients tested. No patient showed evidence of renal disease.

Other Types of Muscular Disorder

In the present study thyrotoxicosis associated with a true myopathy was not seen. A diagnosis of myasthenia gravis was occasionally considered but was dismissed on clinical grounds and after testing with edrophonium chloride or neostigmine. None of the patients showed the features of periodic paralysis or of Parkinsonism.

External ophthalmoplegia was not outstandingly severe in the patients in this series with thyrotoxic muscular weakness. Ophthalmoplegia in a mild form was observed in nine of the patients. The degree of ophthalmoplegia and its incidence was unrelated to the severity of muscular weakness elsewhere; it was absent in some of the patients with the most severe generalized muscular weakness, and it did not respond consistently to antithyroid treatment.

Treatment

Treatment of the muscular lesion in thyrotoxicosis was found to be equally effective by all forms of antithyroid therapy. Generally the muscular lesion did not demand urgent treatment in itself, and improvement was quite rapid after all forms of therapy. When the weakness is unusually severe iodine is probably the method of choice, being the most quick-acting; in Case 3 rapid recovery occurred after 10 days. Relapse of thyrotoxicosis sometimes, but not invariably, resulted in a return of the muscular weakness.

Case Histories

Case 1.—A man aged 21 became ill with fever, heart failure, and tachycardia not responding to digitalis. There were no eye signs or thyroid enlargement. After four months there was a rapid onset of muscular weakness, at first with aching, in all four limbs and also the bulbar muscles, with loss of reflexes but no sensory involvement. B.M.R. was +37%. Muscle biopsy showed widespread degeneration of muscle fibres with foci of lymphocytes. Treatment with iodine was begun two months after the onset of muscle weakness, during which time there had been little change. After a month there was considerable recovery; he could walk again and the reflexes returned; B.M.R. +16%. After nine months he relapsed and thyroidectomy was carried out, followed by rapid and apparently complete recovery of both heart and muscles. Two years later he developed heart failure again, with little recurrence of muscle weakness, and died. At necropsy the only positive finding was cardiac enlargement.

Case 2.—A youth aged 19 presented with an illness of rapid onset, the main features of which were psychotic disturbance, extreme muscular weakness with pain in the legs and paraesthesia, loss of tendon reflexes, unimpaired swallowing and respiration, and loss of 28 lb. (12.7 kg.) in weight. There was diffuse enlargement of the thyroid, but eye signs were absent. The electromyograph was characteristic of myopathy. Treatment with thiouracil was begun after the situation had remained unchanged for two months; improvement started after 10 days and was rapid. Three months later the symptoms and signs had almost disappeared and the electromyograph was nearly normal. Treatment was continued for a year; two years later he was well and had no muscular weakness.

Case 3.—A man aged 52 had increasingly severe cardiac failure for a few weeks; he lost 28 lb. (12.7 kg.) in weight and had exophthalmos and lid-lag but no external ophthalmoplegia. He was admitted to hospital, and after a few days his muscular weakness, slight on admission, rapidly increased and wasting became apparent. The face and bulbar muscles were involved, but there was no serious difficulty in swallowing or respiration. The tendon reflexes were quick. The electromyograph showed a myopathic pattern. He was treated with iodine and thiouracil concurrently; the muscular weakness showed a dramatic improvement, starting after about 10 days and rapidly recovering. Thyroidectomy was carried out later.

Discussion

A lesion of the skeletal muscles, mainly centripetal in distribution, often accompanies hyperthyroidism, sometimes being a very severe feature of the disease. The lesion has been called thyrotoxic myopathy, and the fully developed chronic form somewhat resembles true myopathy clinically as well as electromyographically, but it is reversible, being closely linked with the state of hyperthyroidism.

Besides the general muscular lesion described, various other locomotor disorders occur in thyrotoxicosis.

External ophthalmoplegia is common, but in the present study there was no correlation between this and the general muscular weakness, suggesting that the two have a different mechanism. Myasthenia gravis occurs more often than by chance in thyrotoxicosis, but a causal relationship between the two has always been difficult to demonstrate (Millikan and Haines, 1953), and the muscular weakness and fatigability in hyperthyroidism have been confused with myasthenia gravis. Periodic paralysis has been described, fluctuating with hyperthyroidism (Millikan and Haines, 1953), but the relationship is not clear and periodic symptoms were not observed in the present series. Nor was any relationship between Parkinsonism and hyperthyroidism (Chapman and Maloof, 1956) observed. Generalized myokymia, without gross weakness or wasting, has been described in hyperthyroidism (Harman and Richardson, 1954).

Muscle biopsy was done in Case 1; widespread degeneration with loss of striation in the fibres and foci of lymphocytes were found. Such changes are unspecific, and a variety of findings, including normality, have been reported since Askanazy, in 1898, described atrophy of the muscle fibres with rows of fat cells in between and abnormal nuclei resembling those of giant cells (Adams, Denny-Brown, and Pearson, 1953). Electron microscopy has shown a deposit of homogeneous material containing mucopolysaccharide within the sarcolemma (Iversen, Asboe-Hansen, and Carlsen, 1953), but this change seems unspecific and of doubtful significance. Coërs and Wolff (1959) have described profuse sprouting of subterminal motor-nerve fibres. Electromyography is a useful method of demonstrating the muscle lesion and distinguishing it from the effects of neuropathy and myelopathy, also in assessing the response to injected edrophonium chloride and curare. However, neither histology nor electromyography defines the exact site of mechanism of the muscle lesion. The changes shown are not specific except in their reversibility by antithyroid treatment.

It is likely that the muscle disorder in hyperthyroidism is essentially one of muscle-fibre metabolism, structural and other changes being secondary. The exact nature of this disorder is unknown, but there are some biochemical findings of possible relevance. Zondek (1944) suggested that in hyperthyroidism muscular work was uneconomical in oxygen consumption and was associated with a rise in blood lactic acid due to a failure of glycogen resynthesis. Abnormalities of creatine and creatinine metabolism have been attributed to disordered muscle metabolism.

Creatine is synthesized by the liver, largely taken up by the muscles, and later excreted in the urine as creatinine. If muscle mass is reduced, excess creatine is excreted in the urine and the serum creatine exceeds about 0.6 mg./100 ml.; creatinine excretion is diminished (Milhorat, 1953). Probably this excess creatine excretion is not an indication of the site of the chemical disorder of muscle metabolism, at the stage of phosphocreatine synthesis, but results simply from decreased muscle mass, because similar changes in creatine metabolism are found in normal old age as well as a variety of other conditions with wasted muscles (Zierler, 1951). It has not been found that the change in creatine metabolism accurately reflects the severity of the muscle lesion. Muscle lesions attributed to tocopherol deficiency and potentiated by thyroid have been described in experimental animals, and the possibility that tocopherol deficiency or depletion in clinical hyperthyroidism is related to the muscle lesion has to be considered. Postel (1956) found that there was a close association between a reduced serum tocopherol level and severe hyperthyroidism, but no correlation with the degree of muscle involvement. The results of tocopherol therapy in hyperthyroidism have been indifferent.

The severer muscular lesion in hyperthyroidism is of some importance and should be recognized. Severe muscular weakness of acute onset may be the first symptom of hyperthyroidism, or it may develop rapidly in a patient already hyperthyroid, and the usual symptoms of hyperthyroidism can be partly masked by muscle-weakness. Thyrotoxic myopathy should always be considered as a possible cause when dealing with a patient with muscular weakness, because this dangerous condition is curable. In patients who have the commoner chronic mild muscle lesion with hyperthyroidism a separate cause for the weakness and wasting need seldom be sought and a good prognosis can be given. The muscle lesion is of some value as a confirmatory sign in the diagnosis of hyperthyroidism.

Summary

Twenty-six cases with evidence of a muscular lesion with hyperthyroidism are described.

The muscle lesion occurs in an acute generalized form, which is rare and may not be easily recognized, and in a chronic, more localized form which is probably present to some extent in most patients with hyperthyroidism.

Clinical and electromyographic features of a myopathy are present. The lesion is cured by all forms of antithyroid treatment. It is probably a biochemical one, but its exact nature is not known.

I am indebted to the physicians of St. Thomas's Hospital for permission to describe cases under their care; to Dr. H. J. Anderson for helpful advice and criticism; and to Dr. P. Bauwens for the electromyographic findings.

References

Adams, R. D., Denny-Brown, D., and Pearson, C. M. (1953). *Diseases of Muscle*, p. 467. Hoeber, New York.
Bauwens, P. (1955). *Proc. roy. Soc. Med.*, **48**, 194.
Chapman, E. M., and Maloof, F. (1956). *New Engl. J. Med.*, **254**, 1.
Coërs, C., and Wolff, A. L. (1959). *The Innervation of Muscle*, p. 118. Blackwell, London.
Harman, J. B., and Richardson, A. T. (1954). *Lancet*, **2**, 473.
Iversen, K., Asboe-Hansen, G., and Carlsen, F. (1953). *Acta endocr. (Kbh.)*, **14**, 177.
Lahey, F. H. (1932). *Ann. intern. Med.*, **5**, 1123.
Milhorat, A. T. (1953). *Res. Publ. Ass. nerv. ment. Dis.*, **32**, 400.
Millikan, C., and Haines, S. F. (1953). Ibid., **32**, 61.
Postel, S. (1956). *J. clin. Invest.*, **35**, 1345.
Zierler, K. L. (1951). *Bull. Johns Hopk. Hosp.*, **89**, 263.
Zondek, H. (1944). *The Diseases of the Endocrine Glands*, p. 119. Arnold, London.

New activities and research in the field of cancer, heart disease, atomic energy, and rehabilitation of the physically and mentally handicapped were approved by the 28-nation Regional Committee for Europe at its ninth session in Bucharest, under the chairmanship of Professor V. MARINESCU, Minister of Health and Social Welfare for Rumania. The Committee also adopted a co-ordinated plan establishing priority for the eradication of malaria in continental Europe, in order that total eradication be attained at the latest in 1962. (W.H.O. Euro/104.)

THE EPILEPTIC IN RELATION TO PREGNANCY*

BY

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The modern management of epilepsy, which combines the use of improved anticonvulsants with a more sympathetic attitude towards the disability, encourages the epileptic to live a normal life in the community. Opportunities for the epileptic to marry are increased by the widening of their social contacts, and less emphasis is laid on the risk of direct inheritance of epileptic fits. Pregnancy in the epileptic is therefore likely to become a more common therapeutic problem, and it is important to know what treatment is necessary to control epileptic attacks during gestation.

What is the definition of epilepsy? Williams (1958) has suggested that a patient has epilepsy when the attacks recur without a demonstrable independent cause. General epilepsies consist of petit mal and grand mal, which, although so different in their clinical manifestations, are both forms of genetic epilepsy and show electroencephalographic (E.E.G.) similarities, in that the disturbances are symmetrical and synchronous in the hemispheres. Partial or focal epilepsy is characterized by a focal onset both in the clinical manifestation and in the E.E.G. features. Suter and Klingman (1957) found that focal E.E.G. abnormalities were present more commonly when attacks began with pregnancy than in patients who had a previous history of epilepsy and showed an increase of fits during pregnancy.

Burnett (1946) reviewed the statistics from the literature and stated that about a third of pregnant epileptics showed an increase of fits. The neurologist tends to see patients with gestational epilepsy or those whose epilepsy has increased in severity, and so has the impression that deterioration is the usual result. However, many patients get through a pregnancy without ill effect and occasionally amelioration results, perhaps due to better therapy. Curious case histories are on record in which a patient may have epileptic attacks when pregnant with a male child but not with a female. Endocrine factors have been postulated, but the cause is quite unknown. As might be expected, a patient with menstrual epilepsy, which indicates a sensitivity of the seizure threshold to metabolic changes, tends to have fits in pregnancy, and these may become more severe.

Deterioration in Pregnancy

The exacerbation of a previously unsuspected genetic epilepsy with menstrual manifestations is illustrated by the following case history.

A woman aged 22 suffered from severe dysmenorrhoea associated with a short episode of disturbance of consciousness which had been regarded as a form of faint. When pregnancy occurred it was hoped that it might ultimately prove beneficial for her menstrual disorder. However, she developed major attacks when 22 weeks pregnant, the E.E.G. was characteristic of genetic epilepsy, and a family history of epilepsy was obtained. She was treated by rest, sedation with hydantoinate, and phenobarbitone or methylphenobarbitone, but she was still having two larval attacks weekly when discharged.

Reactivation of an Epileptogenic Focus

After a long period of complete freedom from epileptic attacks, or a single convulsive episode, there may be a recurrence of fits in pregnancy; so it is important to ask for a history of convulsions in the antenatal interview.

A woman aged 34 had a major fit at the age of 14. An uncomplicated pregnancy took place at the age of 26; then at the age of 30 she became pregnant again and developed frequent epileptic attacks. These were preceded by a mood of depression and were associated with an aura of vertigo and visceral disturbance with sweating and pallor, followed by an abrupt loss of consciousness resulting in injury on falling. An E.E.G. showed evidence of a right anterior temporal lobe focus. The attacks persisted after delivery, and the patient has become an epileptic; but whether the pregnancy had a significant effect in reactivating the focus is difficult to decide.

Gestational Epilepsy

Epilepsy may develop in a first or later pregnancy, and the attacks tend to be focal in clinical or E.E.G. manifestations.

A patient aged 41 started to have epileptic attacks during her fifth pregnancy, with a focal onset in the right arm. She was fully investigated to exclude a neoplastic or atrophic lesion, with negative results, and the attacks responded satisfactorily to phenobarbitone.

Fits appearing after a disturbance of consciousness at the time of delivery or in the puerperium may be associated with temporal-lobe attacks, and it is possible that the delivery has resulted in a vascular lesion of the temporal lobe.

A patient was unconscious for 24 hours after her first labour. At the age of 28 she developed attacks in which she felt nauseated, experienced hallucinations of taste, and tended to mutter over and over again, "I have been doing this for years and years." She would stand stiff and still and then have a period of post-epileptic automatism. An E.E.G. showed a generalized dysrhythmia with some fast activity in the left anterior temporal region. During her fourth pregnancy she was admitted with serial major attacks, which were controlled by the addition of phenytoin to her previous sedatives of methylphenobarbitone and phenobarbitone.

Another woman developed temporal-lobe epilepsy two weeks after the birth of her child. The attacks were preceded by a vision of a man in a white coat standing behind her, which she associated with her labour. It is well known that in temporal-lobe epilepsy an experience with an emotional content tends to be revisualized during the course of the attacks, as manifested in this patient.

Metabolic Aspects

The question arises, Which are the metabolic changes occurring in pregnancy likely to trigger off a liability to seizures? The effect of hydration on the epileptic is well known, and the vasopressin diagnostic test employs

*Based on a paper read in the Section of Neurology and Neurosurgery at the Annual Meeting of the British Medical Association, Birmingham, 1958.

this sensitization of the cerebral mechanism as a test of epilepsy. Alteration of the *p*H of the blood towards alkalosis by hyperventilation is a usual technique employed in departments of electroencephalography to reveal abnormal rhythms. Convulsions may also occur as the result or reduction of the serum calcium, sodium, potassium, and magnesium. Klingman (1954) has shown that epileptic patients make a clinical improvement and show a more stable E.E.G. if treated with a moderately low sodium diet and sodium-binding ion-exchange resin to reduce any tendency to hydration.

To summarize, hydration, alkalosis, and reduction of the serum electrolytes are changes which result in seizures in the epileptic and are also changes associated with the pregnant state.

During pregnancy there is a gain in weight, which is in part due to extra water retained in the increased plasma volume and in the intracellular and extracellular tissues. An increase of about 20 to 24 lb. (9 to 11 kg.) is regarded as permissible, and some 10 lb. (4.5 kg.) of this is due to extra water retained. The increase of body fluid in normal pregnancy would favour cerebral instability and the appearance of attacks in the predisposed patient. Any uncontrolled weight gain might have serious implications, and studies on pregnant epileptic patients suggest that a rapid increase in weight usually precedes the appearance of more frequent epileptic seizures.

A reduction of CO_2 in the alveolar blood occurs as a feature of pregnancy with hyperventilation due to an increased sensitivity of the respiratory centres. Although a slight compensatory acidosis is usually maintained, loss of chloride through vomiting may favour an alkalosis. Oral sedatives also may be lost as a result of vomiting. The concentration of sodium, calcium, and magnesium ions tends to be slightly reduced in the serum in the pregnant state, although in the case of sodium the total body content is increased.

Aldosterone secretion is not infrequently increased in pregnancy, and is the hormonal factor which is important in regulating the degree of water and sodium retention and the excretion of potassium. Much work has been done on the significance of this hormone in water and salt retention in the toxaemias of pregnancy, but Barnes and Quilligan (1956) thought that there was no correlation between its level and the severity of the clinical state of the patient. They suggested that the increase in the hormone might be in response to the sodium restriction in the diet rather than a cause of sodium retention.

Status Epilepticus

Hormonal effects with retention of intracellular fluids triggering off the cerebral cortex are postulated as the cause of uncontrollable epileptic phenomena. Status epilepticus is a grave complication, and may develop at any time during pregnancy and labour, or after delivery. Usually an increasing number of major attacks which do not respond to sedation precede the onset of status, but uncontrollable fits may be the first intimation that the patient is dysrhythmic. The mortality is higher than that of eclampsia, from which it requires to be distinguished. The incidence is fortunately low. Klein *et al.* (1956) reported two cases, both fatal, among 52,000 deliveries at the Morrisana City Hospital, New York. Goodwin and Lawson (1947) recorded a recovery in the first trimester of pregnancy, although fits continued for five days. Status epilepticus can be differentiated from eclamptic convulsions by the normal blood pressure and the lack of gross albuminuria and oedema, although there is not uncommonly some slight oedema of the dependent parts of the body before the appearance of the serial fits.

Abnormal Pregnancy

Toxaemia and Pre-eclampsia

Consideration of metabolic and genetic factors is helpful in understanding the close relationship between fits and toxaemia. Recent work on the aetiology of toxaemia has developed along two lines of investigation, both, however, resulting in the same conclusion, that the essential feature is a pressor factor as a common mechanism in the production of the eclamptic picture. McClure Browne (1957) stressed the importance of hypertension as a cause of placental ischaemia, and Morris (1957) found that exercise reduced the rate of the myometrial circulation as shown by sodium isotope clearance. Quantitative improvement of clearance follows rest, so his work confirmed the value of rest in the prevention of eclampsia. Sophian (1957) considered that renal ischaemia was the vital mechanism producing salt and water retention. He suggested that stretch of the uterine wall, which was most likely to occur in first or twin pregnancies activated a utero-renal reflex, resulting in ischaemia of the kidneys. The slowing of circulation in the kidneys produced oedema, increased protein in the urine, and ultimately hypertension.

Hereditary Factors

Burnett (1946) drew attention to the significance of constitutional factors in the relationship between epilepsy and eclampsia. He observed that epilepsy might be inaugurated by eclamptic convulsions and that there was a predisposition towards epilepsy among the relatives of an individual who had fits associated with toxaemia. Patients showed an unequal tendency to fits in eclampsia, although their metabolic disorder might be of equal severity and there appeared no constant relationship between the degree of toxaemia and the clinical manifestation of fits.

Rosenbaum and Maltby (1943) provided E.E.G. confirmation that a cerebral dysrhythmia was important in the production of convulsions, as E.E.G. abnormalities were present in 65% of eclamptics as against 10% in non-convulsive pre-eclamptic patients. The situation seems rather to resemble that of head injury, in that certain individuals exposed to a cerebral disturbance, whether traumatic or metabolic, develop fits if there is a hereditary or constitutional predisposition.

The trigger mechanism generally suggested in toxaemia of pregnancy is a combination of cerebral oedema and of cerebral vasoconstriction. The accepted mode of treatment in pre-eclamptic toxaemia aims at the prevention of increased blood pressure and oedema. The measures, which include rest, a diet with a high protein and low carbohydrate and fat content, and a reduction in salt intake, would also tend to suppress the occurrence of fits in the dysrhythmic subject.

Hypertension and Epilepsy in Pregnancy

Essential hypertension combined with toxaemia of pregnancy may precipitate the appearance of epilepsy.

One woman, at the age of 34, had seven eclamptic fits, associated with high blood pressure and renal dysfunction. Thirteen years later she still suffers from a severe hypertension with focal fits affecting the right side of the body, starting in the right foot, although her E.E.G. was to be correlated with epilepsy. An intravenous pyelogram showed an inactive kidney on the right and a dilute secretion on the left. Treatment with the usual sedatives and, more recently, hypotensive drugs, including mecamylamine, has resulted in a reduction in the number of fits, which formerly occurred many times a day. Here probably is an example of a patient with a basic cerebral dysrhythmia, a focal lesion perhaps of vascular type produced at the time of her toxaemia of pregnancy and a persisting epileptic disorder.

Anaemia in Pregnancy

The blood volume increases during pregnancy and there is a relative increase of blood plasma, which produces a fall in haemoglobin and in cell concentration. An iron-deficiency anaemia is not uncommon, but another complication which may occur is the development of a megaloblastic anaemia. This may be due to pernicious anaemia of pregnancy—a self-limiting condition responding to folic acid—in which the blood returns to normal after delivery. However, the effect of anticonvulsants on blood formation must not be forgotten. Hawkins and Meynell (1958) have described the occurrence of macrocytosis and anaemia in treated epileptics. The abnormality of the red cells was attributed to a competitive inhibition by the drugs of some enzyme process normally involving folic acid as a co-factor, for this vitamin has a general structural similarity to anticonvulsants. It was observed that when anaemia was due to macrocytosis from drugs the administration of folic acid, 10 mg. daily, was followed by a marked improvement in the fits and in the macrocytosis. It is important to have full blood counts carried out during pregnancy to detect the appearance of macrocytosis in epileptic patients on anticonvulsants.

Cerebral Tumour in Pregnancy

The possibility that pregnancy may cause the appearance of focal signs due to a tumour is well known, as Bickerstaff *et al.* (1958) have shown in the case of the meningioma. Increased vascularity of the neoplasm has been suggested as a cause, but Weyand *et al.* (1951) reported actual changes in the cytology of meningiomas. The cytoplasm of the cells was characterized by a foamy appearance, attributed to an increase in intracellular fluid, and there was no evidence of mitosis suggesting an increase in number. These findings would explain the appearance of convulsions and focal signs in pregnancy.

General Management

A direct request for a personal or family history of disturbances of consciousness should be made to the patient and, if possible, also to relatives. If a patient has been free from epileptic attacks for some years sedatives may have been discontinued and she may forget to mention that she has had an epileptic tendency. The indications for anticonvulsants are the same as in the non-pregnant epileptic, phenobarbitone, ½–1 gr. (32–64 mg.), or phenytoin, 0.1 g., two or three times a day, being useful in major or focal epilepsy. Primidone, 0.25 g., may be used in combination with phenytoin for major attacks instead of phenobarbitone if the response has not been satisfactory. A drug of the dione group, 0.3 g. three times a day, may be required for true petit mal. Phenobarbitone in a slowly absorbed form (" spansule "), given at night, may carry the patient over the morning hours when retention of tablets is difficult owing to vomiting. It may be necessary to give sodium phenobarbitone, 3 gr. (0.2 g.), by injection to maintain the anticonvulsant level during vomiting or at the time of delivery.

Avoidance of an excessive gain in weight during pregnancy is a matter for close co-operation with the obstetrician. Rest in bed, restriction of salt, and a high-protein, low-carbohydrate, low-fat diet are employed, or, alternatively, as is used in America, a combination of a low-calorie diet, restriction of salt, with acetazolamide (" diamox "), 250 mg. b.d. This diuretic is a powerful inhibitor of the enzyme carbonic anhydrase, an action which results in a loss of bicarbonate. The systemic acidosis produced has been thought by some workers, including Suter and Klingman (1957), to make acetazolamide particularly appropriate in the treatment of retention of fluid in pregnancy with increase in epileptic attacks. Alternatively, a sodium-binding ion-exchange resin may be used to prevent retention of sodium. Suter and Klingman report good results with " resodec," 15 g. two or three times a day for periods of a fortnight, to reduce any excess weight gained. The use of the oral diuretic chlorothiazide has been investigated by Watson *et al.* (1958) in pre-toxaemia; they found that an oral dose of 2 g. produced a substantial diuresis in six hours, but was without effect on the blood pressure. This may prove a valuable drug, but further clinical experience is necessary.

Hypertension and fits complicating pregnancy indicate the use of a hypotensive drug from the point of view of control of the epilepsy as well as the hypertension. It is of interest that McClure Browne and his colleagues (Kincaid-Smith *et al.*, 1958) have managed a pregnancy successfully in a severely hypertensive patient with the use of pentolinium, 40 mg. t.d.s. by injection, followed by mecamylamine, 10 mg. b.d., with reserpine (" serpasil "), 0.1 mg. t.d.s. orally. Maintenance of the erect posture then is important instead of rest.

Both iron-deficiency and macrocytic forms of anaemia should be treated. The usual treatment for the latter, provided the case is not one of true pernicious anaemia, is folic acid, 10 mg. b.d. It may be necessary to employ packed-cell transfusions where there is a severe iron-deficiency anaemia or a low nutritional level with anaemia associated with fits.

Status epilepticus may be guarded against by admission of any patient whose attacks cannot be satisfactorily controlled and whose serial E.E.G.s show deterioration. Paraldehyde, 5 ml. intramuscularly, may be given two-hourly, or sodium phenobarbitone, 3 gr. (0.2 g.) subcutaneously. Hospital procedures include intravenous thiopentone, sodium phenytoin, and, in severe cases, D-tubocurarine combined with controlled respiration. Termination of pregnancy by surgical induction may be indicated (Burnett, 1946).

Where fits may be symptomatic it is important to examine the nervous system carefully for focal signs. Investigations for a neoplasm include *x*-ray films of the skull and chest, and an E.E.G.; admission for contrast radiography may be necessary.

Summary

As a result of better therapeutic and social management the epileptic woman has increased opportunities of marriage and epilepsy is likely to become a more frequent complication of pregnancy.

The effect of pregnancy on the epileptic is unpredictable. The attacks may increase in number or remain unchanged. Reduction in incidence of fits is often related to better therapy. Epilepsy associated with menstruation usually persists in pregnancy. When attacks first appear in pregnancy (gestational epilepsy) these are likely to be partial or focal in character.

The metabolic changes in pregnancy—hydration, hyperventilation, and dilution of calcium, sodium, and magnesium in the serum—favour an increase of fits. The variations in excretion of aldosterone are probably compensatory to fluctuation in sodium intake. Excessive gain in weight and sodium retention may precede the onset of increased fits.

A genetic or constitutional factor is important in the appearance of seizures in toxaemia of pregnancy. A persistent epileptic tendency may result. Status epilepticus is a rare but grave complication, especially when occurring in later pregnancy, and has a higher mortality than eclampsia. The onset of status in pregnancy may be the first manifestation of a cerebral dysrhythmia.

The epileptic woman should not be discouraged from pregnancy unless the attacks are difficult to control in the non-pregnant state, but there is no excuse for regarding this complication of pregnancy lightly. Antenatal care should be as thorough as in suspected toxaemia of pregnancy.

Management of pregnancy consists of suitable anticonvulsants, with dosage corrected for gain in weight. Phenobarbitone in capsule form (" spansule ") may be useful in vomiting of pregnancy. Anaemia should be treated, and macrocytic forms, whether due to pregnancy or anticonvulsants, will require folic acid. Excessive gain in weight should be controlled by diet, restricted salt intake, and rest. If the response is unsatisfactory the use of acetazolamide or ion-exchange resins should be considered. Status epilepticus may require the use of continuous intravenous anticonvulsants, with controlled respiration.

Investigation of gestational epilepsy to exclude a neoplasm may be indicated.

REFERENCES

Barnes, A. C., and Quilligan, E. J. (1956). *Amer. J. Obstet. Gynec.*, **71**, 670.
Bickerstaff, E. R., Small, J. M., and Guest, I. A. (1958). *J. Neurol. Neurosurg. Psychiat.*, **21**, 89.
Browne, J. C. M. (1957). *Proc. roy. Soc. Med.*, **50**, 787.
Burnett, C. W. F. (1946). *J. Obstet. Gynaec. Brit. Emp.*, **53**, 539.
Goodwin, J. F., and Lawson, C. W. (1947). *Brit. med. J.*, **2**, 332.
Hawkins, C. F., and Meynell, M. J. (1958). *Quart. J. Med.*, **27**, 45.
Kincaid-Smith, P., Somers, K., and Browne, J. C. M. (1958). *Lancet*, **1**, 508.
Klein, M. D., Goodfriend, M. J., and Shey, I. A. (1956). *Amer. J. Obstet. Gynec.*, **72**, 188.
Klingman, W. O. (1954). *Amer. J. Psychiat.*, **111**, 184.
Morris, N. (1957). *Proc. roy. Soc. Med.*, **50**, 788.
Rosenbaum, M., and Maltby, G. L. (1943). *Arch. Neurol. Psychiat. (Chicago)*, **49**, 204.
Sophian, J. (1957). *Proc. roy. Soc. Med.*, **50**, 790.
Suter, C., and Klingman, W. O. (1957). *Neurology (Minneap.)*, **7**, 105.
Watson, W. C., Thomson, T. J., and Buchanan, J. M. (1958). *Lancet*, **1**, 1199.
Weyand, R. D., McCarty, C. S., and Wilson, R. B. (1951). *Surg. Clin. N. Amer.*, **31**, 1225.
Williams, D. (1958). *Brit. med. J.*, **1**, 661.

A PRELIMINARY REPORT ON CHLORPROMAZINE IN TETANUS

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Prior to the work of Hougs and Andersen (1954) and Kelly and Laurence (1956) it had been shown by Courvoisier *et al.* (1953) that chlorpromazine antagonizes some central convulsant drugs and prolongs the effect of relaxant drugs like D-tubocurarine and mephenesin. Dasgupta and Werner (1955) showed that it inhibits motor activity induced by cortical stimulation in cats and also suppresses the postural responses which occur on stimulation of cerebellar cortex and reticular formation; and its paralytic effect on skeletal muscles was demonstrated by Burn (1954). It was these qualities of chlorpromazine, together with its better-known qualities as a sedative, a tranquillizer, and as a potentiator of other hypnotics and sedatives, which probably suggested its rational use in tetanus. It was used in mild cases or as a useful adjunct by Adriani and Kerr (1955), Bodman *et al.* (1955), and Cole and Robertson (1955), and it is interesting to note that Andersen *et al.* (1955) regarded it as a failure. It is apparent that a dosage on the small side was used by them. Laurence *et al.* (1958) described their results in 37 cases. Success in individual cases, both serious and unusual, was also reported by Barr (1958), Packard *et al.* (1958), Azmi (1958), and Hutchinson and Hurrell (1958). Johnstone (1958) describes rather unfavourable results with small doses of chlorpromazine and amylobarbitone in 17 patients, 11 of whom died.

Adams (1958) reported the results of a carefully controlled clinical trial of chlorpromazine, chloral hydrate, and barbiturates in the treatment of nearly 200 patients of tetanus. His impression was that a mixture of barbiturates and chlorpromazine was better than any other drug alone, and he stressed that smaller doses of each could be given. He slightly preferred barbiturates for the treatment of neonatal cases, but thought that chlorpromazine could dramatically control the laryngeal spasm and could be given intravenously.

Laurence (1958) has reported that phenothiazine derivatives like chlorpromazine were by far the best in abolishing spasm and were superior to centrally acting relaxants like mephenesin.

We have been using chlorpromazine in the management of tetanus cases for some time at Hamidia Hospital, Bhopal. We have so far given a smaller dose than Laurence *et al.* and have occasionally used paraldehyde as an adjunct. This method gave us a very favourable clinical impression and prompted us to publish this preliminary report on 30 cases. The trial is still going on, and we propose to publish a report on a bigger series later on.

Method and Material

Patients were divided into two groups at random—one group receiving chiefly chlorpromazine while the other received only paraldehyde.

TABLE I

Case No.	Sex	Age	Incubation Period in Days	Period of Onset in Hours	Severity	Total Duration of Stay in Hospital in Days	Result	Day of Administration of Serum after Onset	Evidence of Sepsis
				Chlorpromazine Group					
1	F	4 years	—	6	+	15	Cured	1	Nil
2	F	10 ,,	20	2	+++	20	,,	3	Septic injury left foot
3	M	2 ,,	—	6	+++	2	Expired	2	Bronchopneumonia
4	F	20 ,,	5	24	+++	10	Cured	1	Puerperal sepsis
5	F	4 ,,	8	10	+++	19	,,	8	Otitis media
6	M*	8 days	5	48	+++	1	Expired	4	Nil
7	F	16 years	9	8	+++	8/24	,,	3	Puerperal sepsis
8	F	20 ,,	9	6	+++	30	Cured	6	,, ,,
9	F	22 ,,	2	5	+++	30	,,	13	,, ,,
10	F†	22 ,,	4	10	+++	15	,,	4	Nil
11	M	3 ,,	10/24	4	+++	14	,,	3	Septic injury left toe
12	F	25 ,,	8/24	2	+++	16	,,	8	Puerperal sepsis
13	M	12 ,,	4	48	++	12	,,	4	Nil
14	M	40 ,,	—	8	++	7	,,	15	,,
15	M‡	20 ,,	4	6	+++	15	,,	2	,,
				Paraldehyde Group					
1	M	9 years	4	48	+	30	Cured	4	Nil
2	M	15 ,,	7	48	+	15	,,	7	Otitis media
3	M§	22 ,,	3	20	++	5	Expired	4	Septic injury
4	M	12 ,,	5	16	++	3	,,	1	Leucocytosis
5	M	25 ,,	2	24	+++	3	,,	5	Septic injury
6	F	26 ,,	1	12	+	30	Cured	4	,, ,,
7	M	30 ,,	30	24	+	30	Expired	2	Whitlow ,,
8	F	40 ,,	—	10	+++	4	,,	1	Nil
9	M	27 ,,	4	20	+++	30	Cured	1	Septic injury
10	M*	11 days	9	10	+++	6	Expired	4	Nil
11	F	24 years	—	25	++	15	Cured	5	,,
12	M*	6 days	6	10	++	2	Expired	6	,,
13	M‖	8 years	1	24	+	20	Cured	6	,,
14	F‖	3 ,,	8	48	++	16	,,	9	,,
15	M‖	6 ,,	3	24	++	13	,,	4	,,

* Tetanus neonatorum.
† 300,000 units of A.T.S. given.
‡ Prophylactic dose of 3,000 units of A.T.S. given one day after injury.
§ Patient left against medical advice, treated as expired, as the condition had deteriorated during the stay in hospital.
‖ Patient left against medical advice, treated as cured because the spasms and rigidity had disappeared during the stay in hospital.

Selection of Cases.—The trial was made on patients admitted to the Hamidia Hospital with a clinical diagnosis of tetanus. One or other treatment was given at random without any reference to the severity of disease or the age group of patients. All other treatment given to both groups was standardized.

TABLE II.—*Comparison of Chlorpromazine and Paraldehyde Group*

No.	Chlorpromazine Group			Paraldehyde Group		
	Average	Max.	Min.	Average	Max.	Min.
Duration of onset (hours)	13	48	2	24	48	10
Incubation period (days)	5 22 24 *(12/15)	20	8 24	6 10 24 *(13 15)	30	1
Days in hospital of survived cases	17·0	30	7	21	30	13
Days in hospital of fatal cases	1	2	8 24	8	30	2
Age	14·4 yrs.	40 yrs.	8 days	16·46 yrs.	40 yrs.	6 days
Age (non-neonatal cases)	15·57 yrs.	40 yrs.	2 yrs.	19 yrs.	40 yrs.	3 yrs.
	No. of Cases	Percentage		No. of Cases	Percentage	
Male	6	—		11	—	
Female	9	—		4	—	
Severity group:						
Mild	1	—		5	—	
Moderate	2	—		6	—	
Severe	12	—		4	—	
Cure rate	15	80%		15	53%	
Cure rate in 3 severity groups:						
Mild	1	100%		5	80%	
Moderate	2	100%		6	50%	
Severe	12	75%		4	25%	
Mortality rate	15	20%		15	46·6%	
Mortality rate in neonatal cases	1	100%		2	100%	
Mortality rate in patients surviving more than 24 hours	13	7·7%		15	46·6%	
Mortality rate in non-neonatal cases surviving more than 24 hours	13	7·7%		13	38·4%	

* These figures represent the number of cases in which it was known—i.e., 12 15=12 out of 15 cases.

Standardized Treatment. — Immediately after admission each patient was put to bed in a dark room and was sedated with paraldehyde or chlorpromazine as decided upon at random. The drugs were given intramuscularly in all cases. A test dose of 800 I.U. of antitoxin was given subcutaneously (except in neonatal cases), and if no reaction occurred in half an hour, 100,000 units of antitoxin was administered intramuscularly and 100,000 units intravenously. If a wound was present it was dressed.

Chemotherapy.—Procaine penicillin, 400,000 units, was given intramuscularly daily to adults, and crystalline penicillin, 200,000 units twice daily intramuscularly to infants, for five days.

Feeding.—Nasal feeding was started only if patients could not swallow. Feeding was begun with egg-and-milk mixture.

Drug Dosage.—(1) *Paraldehyde group*:—In this group adults were given 6 ml. of paraldehyde intramuscularly six-hourly or four-hourly according to the severity and frequency of convulsions. The frequency of injections was gradually tapered off as the condition of the patient improved. For children and infants 2–3 ml. of paraldehyde was used. (2) *Chlorpromazine group*:—After an initial dose of 100 mg. adults were given 50–100 mg. of chlorpromazine intramuscularly, depending on severity of spasms. For infants a dose of 25 mg. twice daily was administered. If the spasms recurred in between, paraldehyde 3–6 ml. intramuscularly was sufficient to control them.

Criterion of Severity of Tetanus.—The cases were classified as follows: (1) mild—rigidity present without any spasm, shown in Table I as +; (2) moderate—one to four spasms daily, shown in Table I as ++;

and (3) severe—more than four spasms daily, shown in Table I as + + +.

Duration.—The drugs were continuously administered till the rigidity had almost disappeared and the mouth could be opened fully.

The results are shown in Tables I and II.

Discussion

Although the number of cases was too small for statistical analysis a definite clinical impression was formed that a change over to chlorpromazine from paraldehyde treatment would be advisable, because it controls the spasms better and because it seems to us that it has helped to reduce the mortality. It is generally known that a comparison of mortality figures from different centres may be misleading, because of differences in nursing standards, which are of great importance. Nevertheless, a reduction in the mortality rate achieved at one institution should be a useful pointer to the efficacy of a new regime. With this background the following analysis seems worth recording.

Spasms.—The reflex spasms were dramatically controlled by chlorpromazine within half an hour of the intramuscular administration, and did not recur again before four hours in any case. Even if they reappeared they were transient and very mild, and were easily abolished by 4 ml. of paraldehyde given intramuscularly on occasions to some cases only. On these occasions only paraldehyde, and not additional chlorpromazine, was administered. In the paraldehyde group the spasms were not controlled so efficiently, and continued intermittently for a long time or until death.

Mortality.—Since the use of chlorpromazine it has been our feeling that the mortality rate has been much reduced. Though we appreciate that the number of cases is too small to be of any statistical value, yet one cannot fail to notice that in the chlorpromazine group of 15 cases there were only three deaths (20%). Of these three fatal cases, one (No. 6) was a neonatal case, another (No. 7) was in the hospital for about eight hours only and could hardly be said to have received any substantial treatment. If these two cases are excluded there is only one death out of 13 cases (7.7% mortality), 10 of which were serious. On the other hand, out of 15 patients in the paraldehyde group 7 died (46.6%); even if 2 neonatal cases (Nos. 10 and 12) are excluded there are 5 deaths out of 13 cases (38.4% mortality). The difference in mortality figures in the two groups speaks for itself, and in the non-chlorpromazine group the figures compare with those generally recorded in this hospital as well as those of Laurence *et al.* (52% non-neonatal and 71% neonatal) and Johnstone (56% and 52% in paraldehyde and amylobarbitone groups), and those quoted by various other workers. Johnstone, in his extensive series of 100 cases, has shown that the only consistent feature in 45% of fatal cases was that they all had reflex spasms which continued until death. All the factors which modify mortality occurred to the same extent in both our groups, and we feel that a quick control of spasms has helped to reduce the mortality rate in the chlorpromazine group.

Incubation Period.—The average incubation period was a little less in the chlorpromazine group, and this is consistent with the fact that there were more serious cases in the chlorpromazine group. Cases with an incubation period under nine days are known to be of a serious nature, and this was confirmed in both our groups.

Period of Onset.—Cases with a period of onset less than 48 hours are known to have a graver prognosis. The average period of onset in the chlorpromazine group was shorter by 11 hours than that in the paraldehyde group, yet the mortality rate was reversed.

Toxicity and Complication of Drugs.—The highly irritant action of chlorpromazine described by Laurence *et al.*, causing induration of muscles, was not our experience, probably because of the low doses and infrequent injections administered by us. Similarly, the mental confusion and Parkinsonian tremor described by Packard *et al.* has not been seen in our cases so far.

Dosage Used.—We feel that 100 mg. of chlorpromazine, given immediately, followed by 100 or 50 mg. 12-hourly, may just be enough to control the spasms in adults. If, however, the spasms recur in between, 4 to 6 ml. of paraldehyde, given occasionally intramuscularly, will control them in most cases. We also feel that the high doses used by Laurence *et al.* in their series may be unnecessary and hazardous. Children and infants may be given proportionately smaller doses depending upon their weight and size.

Neonatal Cases.—As there were only three neonatal cases in this series they were not grouped separately. All three patients died in spite of the choice of therapy.

Summary

Chlorpromazine was administered to 15 cases of tetanus; most of them were serious.

The results were compared with those in 15 patients who were treated with paraldehyde. Results with chlorpromazine have been highly satisfactory, and a cure rate of 92.3% has been recorded in chlorpromazine-treated non-neonatal cases that survived more than 24 hours in hospital.

In the chlorpromazine group the drug was administered in comparatively small doses (50 to 100 mg. twice daily intramuscularly for adults), and paraldehyde was occasionally used as an adjunct.

We thank Professor S. M. Misra for permitting us to include three of his cases in this series.

References

Adams, E. B. (1958). *Brit. med. J.*, **1**, 1350.
Adriani, J., and Kerr, M. (1955). *Sth. med. J. (Bgham, Ala.)*, **48**, 858.
Andersen, E. W., Johansen, S. H., and Hougs, W. (1955). *Dan. med. Bull.*, **2**, 84.
Azmi, M. B. (1958). *Brit. med. J.*, **1**, 1176.
Barr, M. N. (1958). *Lancet*, **1**, 991.
Bodman, R. I., Morton, H. J. V., and Thomas, E. T. (1955). Ibid., **2**, 230.
Burn, J. H. (1954). *Proc. roy. Soc. Med.*, **47**, 617.
Cole, A. C. E., and Robertson, D. H. H. (1955). *Lancet*, **2**, 1063.
Courvoisier, S., Fournel, J., Ducrot, R., Kolsky, M., and Koetschet, P. (1953). *Arch. int. Pharmacodyn.*, **92**, 305.
Dasgupta, S. R., and Werner, G. (1955). Ibid., **100**, 409.
Hougs, W., and Andersen, E. W. (1954). *Acta Pharmacol. (Kbh.)*, **10**, 227.
Hutchinson, J., and Hurrell, G. D. (1958). *Brit. med. J.*, **2**, 429.
Johnstone, D. D. (1958). Ibid., **1**, 12.
Kelly, R. E., and Laurence, D. R. (1956). *Lancet*, **1**, 118.
Laurence, D. R. (1958). *Brit. med. J.*, **1**, 1350.
—— Berman, E., Scragg, J. N., and Adams, E. B. (1958). *Lancet*, **1**, 987.
Packard, R. S., Cartmill, T. B., and Henry, J. G. (1958). *Brit. med. J.*, **1**, 16.

ANAEMIA IN THE ELDERLY

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The literature on haemoglobin levels in the elderly is conflicting and apparently varies with the population studied. Howell (1950) found high values and little anaemia in a group of elderly patients in a hospital for the chronic sick. Monroe (1951) found a much higher incidence of anaemia in patients over the age of 61 in a geriatric hospital. Hobson and Blackburn's (1953) survey of elderly people living alone or with spouse showed that 6.5% of women over the age of 60 and 5.1% of men over the age of 65 had haemoglobin levels below 80% Haldane. In the area in which I practise anaemia appears to be more common. The practice, of which I am junior partner, is a rural and semi-urban one, very widely scattered over about 120 square miles (310 square km.). About half my patients live in a small seaside town of 5,000 inhabitants, and half in the surrounding countryside.

Basis of the Survey

Of a total of 275 patients who were aged 65 or over on August 18, 1956, 256 (101 men and 155 women) had blood samples taken. The estimations were made between July, 1955, and December, 1956. During this period eight patients (five men and three women) refused to have a blood sample taken, seven (five men and two women) died, and four (two men and two women) left the practice before estimations could be performed.

Haemoglobin was estimated by the M.R.C. grey wedge photometer (King *et al.*, 1948) on oxalated venous blood. Other haematological estimations found necessary were carried out in the usual way. A level of 80% (Haldane haemoglobin standard, 100% = 14.8 g./100 ml.) (King *et al.*, 1947) or under was taken as pathological and the patients were investigated further.

Patients were grouped according to the Registrar-General's classification (General Register Office, 1956), and a survey classification was also employed, based on the apparent material comfort of the persons concerned. Patients were also grouped into those living alone or not.

Treatment of Anaemic Cases

At first ferrous gluconate was used as the routine oral iron preparation, but ferrous sulphate was substituted later. There were no cases of intolerance of ferrous sulphate in the 10 patients with anaemia for whom it was prescribed. In this survey poor nutrition appeared to be a major factor in the female cases of anaemia, and supplements of ascorbic acid and vitamin-B complex were prescribed for the majority of anaemic patients.

Three patients whose anaemia did not seem to respond to oral iron were treated with parenteral iron preparations.

The anaemia in four patients (three men and one woman) was taken to be irreversible (two had inoperable carcinoma, one had leukaemia, and the fourth had left the district before follow-up). Treatment of the other cases of anaemia produced a rise in haemoglobin, and to facilitate comparison with other surveys the results were calculated on two sets of values: (1) the uncorrected haemoglobin levels (the values obtained from the initial blood samples in the patients studied); and (2) the corrected haemoglobin levels (for these the irreversible cases of anaemia were excluded; the levels achieved after treatment of the "anaemic" cases—those where the haemoglobin was less than 80%—and the original values for the non-anaemic cases were used).

Results

Anaemia

Five men (5%) and 20 women (13%) had haemoglobin levels below 80% (11.84 g./100 ml.). Anaemia in men is usually of serious significance (Brown, 1956), and this the survey confirmed. In two men the anaemia appeared to be due to carcinoma, in one to leukaemia, in one to Addisonian anaemia, and in one to a bleeding duodenal ulcer.

The incidence of anaemia in women (13%) is much higher than that found in Hobson and Blackburn's (1953) survey (5%). In 10 cases the anaemia appeared to be due to poor nutrition, in four to haemorrhage, in two to haemorrhage and poor nutrition, in one to haemorrhage and arthritis, in one to haemorrhage and carcinoma, and in one to Addisonian anaemia; in one case the cause was unknown, the patient having left the district.

None of the female patients in whom poor nutrition was believed to play a major part in the production of their anaemia had any symptoms related to the gastro-intestinal or genito-urinary tracts; clinical examination was negative; all responded to oral iron, and one year later had not relapsed.

Haemoglobin and Age

The haemoglobin level in men gradually decreased with increasing age, though the rate of decrease was not constant. The mean (corrected) haemoglobin level of three unequal age groups was:

Age 65–70 years	..	98.4% (14.5 g./100 ml.)
Age 71–82 „	..	95.7% (14.2 g./100 ml.)
Age 83+ „	..	92.4% (13.8 g./100 ml.)

In women the haemoglobin level gradually increased with increasing age, though the rate of increase was not constant. The mean (corrected) haemoglobin level of the three unequal age groups was:

Age 65–70 years	..	91.0% (13.5 g./100 ml.)
Age 71–82 „	..	92.2% (13.6 g./100 ml.)
Age 83+ „	..	94.3% (14.0 g./100 ml.)

At the age of 65 the mean (corrected) haemoglobin level in men was significantly higher than that in women, but with increasing age the level in men decreased, and in women increased, until at the age of 74 significant differences disappeared.

The gradual decrease in the haemoglobin of men with increasing age is widely accepted, and several workers have shown a gradual increase in that of women (Committee on Haemoglobin Surveys, 1945; Olbrich, 1947); though other surveys have shown a decrease in the women studied as well as in the men (Hobson and Blackburn, 1953; Walsh *et al.*, 1953).

The disappearance of significant difference between the haemoglobin levels of men and women in extreme age has been established in other reports (Olbrich, 1947; Hawkins *et al.*, 1954; Gillum and Morgan, 1955).

Haemoglobin and Sex

Mean haemoglobin levels for men and women were:

Men		
Uncorrected levels	..	94.83% (14.03 g./100 ml.)
Corrected levels	..	96.71% (14.31 g./100 ml.),

with a standard deviation of 7.09 and a standard error of the mean of 0.72

Women

Uncorrected levels .. 89.44% (13.24 g./100 ml.)
Corrected levels .. 91.90% (13.60 g./100 ml.),
with a standard deviation of 7.07 and a standard error of the mean of 0.57

For both the uncorrected and corrected values the means for men and women differ significantly at the 0.001 level of confidence.

There is considerable evidence that sex hormones play a part in the difference between the red-cell and haemoglobin level in lower male and female animals (Vollmer *et al.*, 1939; Domm *et al.*, 1943; Finkelstein *et al.*, 1944). Evidence in man, however, is conflicting (Widdowson and McCance, 1936; Vahlquist, 1950).

A hypothesis that a proportion of women are anaemic by the time of the menopause by reason of menstruation or repeated pregnancies, and that because of inadequate diet the iron-deficiency is not restored afterwards, would explain much of the data of this and other surveys. In this survey the differences in frequency of anaemia were significantly higher in women than in men ($P<0.05$). If an arbitrary level above the 80% Haldane used in this survey (say 90%) had been chosen, and patients below this level investigated and treated, the difference in mean haemoglobin levels between men and women would, I think, have been narrowed further.

Haemoglobin and Living Alone

In this survey women living alone were found to have significantly lower haemoglobin levels than those not living alone. The mean uncorrected haemoglobin level for women living alone was 85.98% (12.73 g./100 ml.) and for women not living alone 90.90% (13.45 g./100 ml.). This difference was significant ($t=2.66$, $P<0.01$).

Corrected haemoglobin levels, where the significant differences between the sexes in age, incidence of anaemia, and frequency of living alone were also taken into account, also showed a significant difference, the mean haemoglobin level for women living alone being 89.26% (13.21 g./100 ml.), and for women not living alone 92.64% (13.7 g./100 ml.); difference significant at 0.05 level ($t=2.4$, $P=0.02$).

The mean (uncorrected) haemoglobin level for men living alone (90.30% = 13.3 g./100 ml.) was not quite significantly lower at the 0.05 level of confidence (P approximately 0.10) than for men not living alone (95.33% = 14.11 g./100 ml.).

Corrected haemoglobin levels also showed no significant difference, the mean haemoglobin level for men living alone being 95.9% (14.19 g./100 ml.) and for men not living alone 93.3% (13.81 g./100 ml.) ($t=1.08$, $P=0.30$).

It is not likely that sex hormone factors could account for the significantly lower haemoglobin levels for women living alone compared with those not living alone. The clinical impression that women living alone are probably the section of the population who care least about proper feeding would do so.

Haemoglobin and Social Class

There was no significant difference in the incidence of anaemia in the various Registrar-General or survey classes, nor in the mean haemoglobin level of men and women in those classes (because of the small numbers involved Registrar-General classes I and II and IV and V were amalgamated for statistical analysis).

Summary and Conclusions

Haemoglobin estimations were performed on 101 men and 155 women over the age of 65 in a general practice. At the age of 65 the haemoglobin levels were significantly higher in men than in women, but with increasing age the haemoglobin level of men gradually decreased, and that of women gradually increased, until at the age of 74 significant differences disappeared.

Five men (5%) and 20 women (13%) had haemoglobin levels below 80% Haldane (11.84 g./100 ml.).

There were no significant differences in haemoglobin levels in the various Registrar-General classes, nor in those of a classification based on apparent material comfort.

In this survey it appeared that a major factor in the high incidence of anaemia in women over the age of 65 was poor nutrition, and it is suggested that it may be a major factor in the difference in haemoglobin levels between the sexes in old age.

I am grateful to Dr. H. F. Barnard and the staff of the Pathology Laboratory, Westwood Hospital, Beverley, who made the haematological estimations, and to Mr. A. B. Royse, Hull University, for help with the statistics.

References

Brown, A. (1956). *Practitioner*, **176**, 434.
Committee on Haemoglobin Surveys (1945). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 252.
Domm, L. V., Taber, E., and Davis, D. E. (1943). *Proc. Soc. exp. Biol. (N.Y.)*, **52**, 49.
Finkelstein, G., Gordon, A. S., and Charipper, H. A. (1944). *Endocrinology*, **35**, 267.
General Register Office (1956). *Census 1951: Classification of Occupations*. H.M.S.O., London.
Gillum, H. L., and Morgan, A. F. (1955). *J. Nutr.*, **55**, 265.
Hawkins, W. W., Speck, E., and Leonard, V. G. (1954). *Blood*, **9**, 999.
Hobson, W., and Blackburn, E. K. (1953). *Brit. med. J.*, **1**, 647.
Howell, T. H. (1950). *Old Age*, 2nd ed., p. 22. Lewis, London.
King, E. J., Wootton, I. D. P., Donaldson, R., Sisson, R. B., and Macfarlane, R. G. (1948). *Lancet*, **2**, 971.
—— Gilchrist, M., Wootton, I. D. P., Donaldson, R., Sisson, R. B., Macfarlane, R. G., Jope, H. M., O'Brien, J. R. P., Peterson, J. M., and Strangeways, D. H. (1947). Ibid., **2**, 789.
Monroe, R. T. (1951). *Diseases in Old Age*, p. 262. Harvard Univ. Press, Cambridge, Mass.
Olbrich, O. (1947). *Edinb. med. J.*, **54**, 306.
Vahlquist, B. (1950). *Blood*, **5**, 874.
Vollmer, E. P., Gordon, A. S., Levenstein, I., and Charipper, H. A. (1939). *Endocrinology*, **25**, 970.
Walsh, R. J., Arnold, B. J., Lancaster, H. O., Coote, M. A., and Cotter, H. (1953). *A Study of Haemoglobin Values in New South Wales*. National Health and Med. Res. Coun. Spec. Rep. Ser., No. 5. Canberra.
Widdowson, E. M., and McCance, R. A. (1936). *J. Hyg. (Lond.)*, **36**, 13.

Medical Memoranda

Congenital Absence of Gall-bladder Associated with a High Caecum and Absence of Ascending Colon

The following unusual case is thought to be of sufficient interest to be put on record.

Case Report

A man aged 45 was first seen in the out-patient department on November 16, 1956, complaining of upper abdominal pain on the right side with some intolerance to fatty food, and flatulence. He was very tender over the gall-bladder and to a lesser degree over the appendix area. Cholecystograms showed no function of the gall-bladder. Examination with the double-dose technique again showed no function of the gall-bladder. The radiologist reported the case as one of gall-bladder disease obliterating the cystic duct.

On admission the patient complained of right-sided abdominal pain of a sharp, gripping character, on and off for

about 12 months, never being longer than three to four weeks without pain. This was often felt in the right hypochondrium, and radiated at times through to the back, but not to the shoulders and was not related to meals. He had no history of jaundice, rigors, or pyrexia associated with the pain. He had not vomited, but the pain nauseated him. He suffered considerably from flatulence, and for the previous 12 months he had tended to suffer from frequent bowel actions with loose stools. There had been no blood or mucus in the stools and there was no history of haematemesis or melaena. There were no symptoms of urinary disease. His appetite was poor and he had lost weight recently.

Intravenous cholangiogram 80 minutes after injection showing the biliary passages and no gall-bladder.

On examination his general condition was good. No abnormal physical signs were found except for some tenderness over the gall-bladder region and over McBurney's point, not nearly so marked as when he was first seen. Cholecystitis with possible subacute appendicitis was provisionally diagnosed.

Operation.—On January 17, 1957, the abdomen was explored through a right subcostal incision, and the gall-bladder was found to be completely absent. There was a narrow, shallow groove on the liver in the position of the gall-bladder fossa. The common bile duct was dissected out and found to be of normal size and not dilated. There was no evidence of a rudimentary cystic duct. A small triangular pad of fat which usually fills the space between the cystic duct and the hilum of the liver contained a small artery which presumably would have been the cystic artery. The caecum was very high in position, lying just beneath the liver and constituting part of the hepatic flexure, so that in fact there was really no ascending colon. The appendix was retrocaecal, pointing upwards and backwards so that its tip was in contact with the liver. It contained a faecalith and was much thickened. The appendix was removed and the abdomen closed.

The histological report stated: "The appendix shows marked fatty infiltration in the submucosa, which is a rather unusual finding. It contains a large faecalith."

On June 24 an intravenous cholangiogram (see Fig.) was carried out and the report stated: "The biliary passages are well visualized in the films taken at 40, 60, and 80 minutes after injection. The right and left hepatic ducts are shown but no evidence of a cystic duct or gall-bladder. No dilatation of the duct is shown and no calculi are demonstrated."

He had been seen several times as an out-patient: his symptoms had completely disappeared, and there had been no recurrence for over six months.

Comment

Gross (1936) reported 38 cases of absence of the gall-bladder with hepatic and common bile ducts normally present and functioning, also 35 other cases of abnormalities of the biliary ducts suggesting atresia, etc. Perusal of the reported cases would suggest that when the gall-bladder is absent the gall-bladder fossa is commonly absent too, but the shallow dimple made by the presence of a rudimentary cystic duct appears to be present in rather less than half the reported cases. The literature suggests that the condition of absent gall-bladder is two or three times as common in the female as in the male.

Smyth (1949) stated that most of the reported cases presented with stones in the common bile duct associated with biliary colic and jaundice. In a number of cases in which stones were not present in the common bile duct the biliary ducts were found not to be dilated as in the present case.

I cannot find any reference in the literature to the carrying out of an intravenous cholangiogram on these patients. It is interesting in that the cholangiogram in the present case showed normal passage of the dye through the bile ducts. I can find only one reference to associated congenital abnormalities in the abdomen with this condition: Rains (1951) described an abnormality of the lesser omentum associated with absence of the gall-bladder.

I thank Mr. H. W. S. Wright for permission to publish this case, Dr. I. Tuck for the histological report, and Dr. A. W. Jenkins for the *x*-ray reports.

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Bibliography

Best, R. R. (1938). *Surg. Gynec. Obstet.*, **66**, 1040.
Caylor, H. D. (1952). *Amer. J. Surg.*, **84**, 352.
Devine, J (1942). *Aust. N.Z. J. Surg.*, **11**, 264.
Finney, G. G., and Owen, J. K. (1942). *Ann. Surg.*, **115**, 736.
Goldenberg, M. M. (1954). *Illinois med. J.*, **105**, 123.
Gross, R. E. (1936). *Arch. Surg. (Chicago)*, **32**, 131.
Mouzas, G., and Wilson, A. K. (1953). *Lancet*, **1**, 628.
Nevill, G. E. (1954). *E. Afr. med. J.*, **31**, 23.
Rains, A. J. H. (1951). *Brit. J. Surg.*, **39**, 37.
Smyth, M. J. (1949). *Lancet*, **1**, 301.
Stolkind, E. (1939). *Brit. J. Child. Dis.*, **36**, 115.

Primary Varicella Pneumonia

Primary varicella pneumonia was first described by Waring *et al.* (1942); since then about 60 cases have been reported in the United States of America (Hampton, 1955; Kriss, 1956; Endress and Schnell, 1956; Weinstein and Meade, 1956; Fitz and Meiklejohn, 1956; Southard, 1956; Tan *et al.*, 1956; Moore, 1957; Krugman *et al.*, 1957), and one of a Hawaiian serving in the American Forces in Germany (Cowley *et al.*, 1956).

No report of the condition occurring in this country has been found in the literature, and it is thought that the following case, which presents similar features, would be of interest.

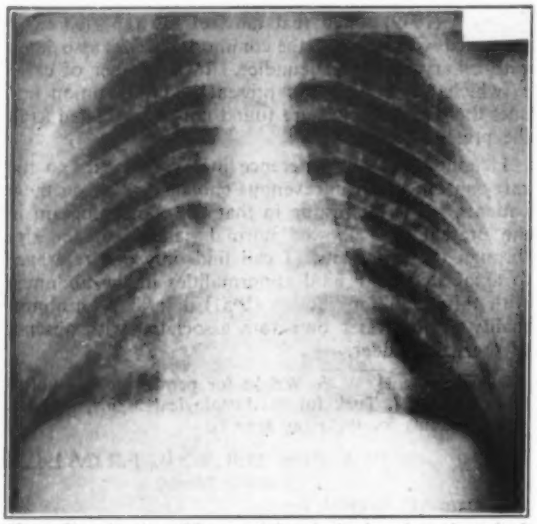
Case Report

A 26-year-old naval rating became ill with malaise and fever. Twenty-four hours later he developed a typical

chicken-pox eruption. His 10-months-old daughter had had chicken-pox three weeks previously. Three days later, while in bed at home, he suddenly became dyspnoeic in the evening and developed a cough with blood-stained sputum. Early next morning he was seen by his doctor, who gave him intramuscular penicillin (1 million units) at once, with oral penicillin V (500 mg.) in the afternoon.

He was admitted to the Royal Naval Hospital, Chatham, the same evening (August 25, 1958). He was moderately ill, with a temperature of 100° F. (37.8° C.), pulse 84, and respirations 24. The rash was severe, almost confluent on the head and trunk, and present also on the buccal mucous membrane. Rales and rhonchi could be heard over both lungs.

Sputum taken next morning was gelatinous and blood-streaked, and grew only normal flora on culture. A portable chest *x*-ray film (he was not well enough to go to the *x*-ray department) showed a diffuse nodular shadowing throughout both lung fields (see Fig.). Intramuscular



X-ray film showing diffuse nodular shadowing throughout both lungs.

penicillin (1 million units b.d.) was continued. The following day the W.B.C. was 11,400 (polymorphs 46%, lymphocytes 45%, monocytes 7%, eosinophils 2%). Chlortetracycline, 1 g. daily, was given in addition.

His temperature settled within 36 hours of admission, and he continued to improve. An *x*-ray film taken on the third day showed the nodular pattern to be still present. Five days after admission there were no abnormal physical signs in the chest, and 10 days later the scabs had cleared completely and the *x*-ray picture of his chest was normal. The results of virus serology are shown in the Table.

Results of Virus Serology

	Influenza			A.P.C. Group	Q Fever	Psittacosis L.G.V.	Agg. Strep. M.G.	Sendai
	A	B	C					
1st specimen, taken 29 8 58	N.T.	N.T.	1/8	1/16	N.T.	1/16	N.T.	N.T.
2nd specimen, taken 8.9.58	1/8	<1/8	<1/8	1/32	<1/8	1/16	<1/16	<1/8

COMMENT

Krugman *et al.* (1957) reported cases of their own and reviewed the literature. They had found the condition in 10 out of 30 adults admitted with chicken-pox over a period of six months.

They describe the disease, which is occasionally fatal, as occurring in adults, with the onset of moderate to severe respiratory distress, two to five days after the skin eruption of chicken-pox. There may be cough, chest pain, dyspnoea, tachypnoea, and frequently cyanosis and haemoptysis. Physical examination reveals signs suggestive of patchy consolidation in both lungs. Chest *x*-ray films reveal a bilateral diffuse nodular infiltration which clears in one to six weeks. There is a normal or slightly raised white-cell count, and no pathogens are found in the nasopharyngeal secretions or sputum. One of their cases came to necropsy, and showed "an extensive haemorrhagic predominantly mononuclear cell pneumonitis, with histological evidence of type A intranuclear inclusion bodies in the pulmonary exudate."

On admission it was thought that our patient was suffering from chicken-pox, complicated by a bacterial bronchopneumonia, but the chest *x*-ray film, sputum, and white-cell count did not suggest this.

The nodular pattern on *x*-ray examination may be found in a large variety of conditions, but had it been a bacterial infection some supporting evidence might have been found in the sputum which contained no pathogens.

The rapid clearing of the radiological abnormality seems to exclude the possibility of this being an incidental finding, and there was no evidence or history of tuberculosis, reticulosis, or cardiovascular disease.

The virus serology showed evidence of a possible recent or past infection with adenovirus. There was a history of an infection of the upper respiratory tract four months previously.

I acknowledge the help and encouragement I have received from Dr. N. Lloyd Rusby and Professor C. F. Barwell, and am grateful to the Medical Director-General of the Navy for permission to publish this report.

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REFERENCES

Cowley, R. G., Crew, W. E., and Hassett, G. R. (1956). *Ann. intern. Med.*, **45**, 518.
Endress, Z. F., and Schnell, F. R. (1956). *Radiology*, **66**, 723.
Fitz, R. H., and Meiklejohn, G. (1956). *Amer. J. med. Sci.*, **232**, 489.
Hampton, A. G., jun. (1955). *A.M.A. Arch. intern. Med.*, **95**, 137.
Kriss, N. (1956). *Radiology*, **66**, 727.
Krugman, S., Goodrich, C. H., and Ward, R. (1957). *New Engl. J. Med.*, **257**, 843.
Moore, R. D. (1957). *Hawaii med. J.*, **16**, 402.
Southard, M. E. (1956). *Amer. J. Roentgenol.*, **76**, 533.
Tan, D. Y. M., Kaufman, S. A., and Levene, G. (1956). Ibid., **76**, 527.
Waring, J. J., Neubuerger, K. T., and Geever, E. F. (1942). *Arch. intern. Med.*, **69**, 384.
Weinstein, L., and Meade, R. H. (1956). *A.M.A. Arch. intern. Med.*, **98**, 91.

Arrangements to co-ordinate tape-recording services for the sick and the blind are now being made at the offices of the British Recording Club, 145, Fleet Street, London, E.C.4. The organizations, which will now work in co-ordination with the British Recording Club, whose journal, the *Amateur Tape Recording Magazine*, now has a circulation of over 50,000 copies, are the Hospital Broadcasting Services, the Tape Reading Circle for the Blind, and the British Recording Club Braille Services.

Reviews

MENTAL STRESS OF OPERATIONS

Psychological Stress. Psychoanalytic and Behavioral Studies of Surgical Patients. By Irving L. Janis. (Pp. 439+xiv. 56s.) New York: John Wiley and Sons, Inc. London: Chapman and Hall Ltd. 1958.

It would have given a better indication of the importance of this book had the author entitled it plainly "Psychological Stress Before and After Surgical Operations." For although Dr. Janis's work was originally designed as a research on the clinical and theoretical aspects of traumatic experiences, his almost exclusive concern with pre- and post-operative reactions renders it a valuable contribution to surgical practice which should be in the hands of all surgeons, dental surgeons, and those general practitioners who carry out minor or major operations on the kitchen table or, as the case may be, in the cottage hospital.

The first half of his book describes the lengthy analysis of a psychoneurotic woman who during its course underwent a surgical operation. Her pre- and post-operative reactions are correlated in detail with her unconscious difficulties and preoccupations, and provide the basis for a number of hypotheses on the effects of stress. If this section should prove a little too technical for the unorientated surgeon or put some strain on his credulity, he will find the second section more to his taste, comprising as it does intensive interviews with 22 patients in a surgical ward together with the results of a questionary applied to 150 male students who had undergone minor or major surgery. A number of conclusions are formulated, of which one of the most significant is that persons who reacted with a moderate level of anticipatory fear were less likely to have a history of psychoneurotic disorder than those who reacted at low or high levels. The "low" group tended to exhibit negative hospital reactions after the operation; the "high" group, although amenable to hospital conditions, experienced a high level of fear during convalescence. The moral is, of course, familiar to experienced surgeons—namely, that the best reassurance for surgical anxieties is a pre-operative understanding of the realities of the situation, which, the author maintains, allows the patient to bind his reality fears to some extent and to understand the subjective nature of his more morbid anxieties. This binding process Dr. Janis describes as "the work of worry," analogous to the "work of grief" carried out by those in a state of mourning.

There are some aspects of this research which might with advantage have been amplified, in particular the sustaining effect of a soundly based positive transference as distinct from the dysphoric effects of a negative transference; also the disturbing influence of a strong unconscious homosexual disposition in male patients. Nevertheless, allowing for this and for some hypotheses that might give rise to divided opinion amongst both surgeons and analysts, the book is an outstanding and stimulating piece of work. Indeed, it is to be hoped that Dr. Janis will follow it up with a booklet written in non-technical language which could be studied by nurses, attendants, and visiting relatives, to say nothing of administrative personnel who guide hospital routines and policies.

EDWARD GLOVER.

SURGERY ILLUSTRATED

An Atlas of Surgery. By F. Wilson Harlow, M.B., B.S. (Durham), F.R.C.S.(Eng.), F.I.C.S. Foreword by Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D., D.Sc., F.R.C.S. (Pp. 363 +xiii; illustrated. 50s.) London: William Heinemann Medical Books Ltd. 1958.

This book is something of a novelty. It contains a collection of between one and two thousand drawings, diagrams, photographs, and radiographs, well reproduced, clearly numbered and lettered, and usefully annotated, for the purpose of imparting an elementary knowledge of the principles and practice of surgery to medical students, nurses, and others who work in surgical wards, casualty departments, and operating theatres. It is meant to supplement the surgical textbook, and an excellent supplement it is. It deals with every branch of surgery and includes a section on surgical pathology. The illustrations are of good quality. A careful examination reveals little to criticize. Illustrations numbered 1214 and 1277 portray very similar lesions; in 1286 the legend is not quite appropriate; and the attempts to illustrate urethritis are not very successful. In 1242 the treatment of meningitis by intrathecal injection of penicillin is mentioned; one would like to see added a note to the effect that the intrathecal dose of penicillin which can be tolerated is very much smaller than that given by other routes.

For those who read surgical books which are not illustrated this atlas will be a godsend; to those who possess well-illustrated textbooks it will be a useful and welcome luxury. The price is reasonable.

ZACHARY COPE.

NEW ZEALAND MEDICAL SERVICES

Official History of New Zealand in the Second World War, 1939–1945. Medical Services in New Zealand and the Pacific. By T. Duncan Stout, M.B., M.S.(Lond.), F.R.C.S.(Eng.), F.R.A.C.S. (Pp. 450+xiv; illustrated. No price.) Wellington, New Zealand: War History Branch, Department of Internal Affairs. 1958.

This volume brings up to date the record of the Medical Services of the New Zealand Army. In a review in this *Journal* (November 2, 1957, p. 1039) of the *New Zealand Medical Services in the Middle East and Italy* the very personal approach to the subject was stressed. This volume continues in the same fashion. Though enclosed in one volume, we really have seven separate and yet interconnected histories which, starting with the picture of the New Zealand medical services in the Pacific, include the story of the growth and development of the medical service of the Navy and Air Force, together with a very interesting account of the trials and tribulations of the New Zealand medical men and others who were unfortunate enough to become prisoners of war. The editor was well served in his attempt to build up the story of the prisoners of war by the personal experiences of two men—Captain Borrie and Brigadier Bull.

The problems of medical organization and administrative control are well displayed. With no standing army and with the merest cadre of part-time medical officers, it redounds to the credit of all concerned, and in particular to Sir Fred Bowerbank, the D.G.A.M.S., that by evolution and gradual development, not at times without severe growing pains, a most efficient medical service was built up. Perhaps the most interesting account of the development is the

story of the disputations which arose over the medical control of the New Zealand sick and wounded. The Army wished to open their own hospitals in the homeland so that they could deal with the problem until a man was either rehabilitated or discharged as unfit for further service. The Home Health Department, on the other hand, insisted that all hospitalization should be a charge on the civilian medical service. Neither side gave way completely, but the heavy guns were with the Governmental Health Department. A workable compromise was eventually reached. In Great Britain we had our problems, too, but with a pre-existing military hospital system we found a quicker and possibly better answer.

The ever-present problem of medical categorization in the armed Forces hit New Zealand just as hard as any of the other nations fighting in war. The ideal solution may not yet have been found, but one based on trying to fit the individual into the job he can do is surely working on the right lines. *Si vis pacem para bellum* is still a sound bit of advice; one trusts, therefore, that the lessons learnt the hard way in the last war will be carefully documented from a volume such as this and lie fully open for the assistance and guidance of those, both soldier and politician alike, who have to plan for the future. The editor and his collaborators are to be congratulated on bringing together a great mass of authentic information. The story, a little discursive at times, is clearly, fairly, and accurately put together in a very readable manner.

J. C. A. DOWSE.

THIRST

Thirst. Physiology of the Urge to Drink and Problems of Water Lack. By A. V. Wolf, Ph.D. (Pp. 536+x; illustrated. 95s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

The author has been studying thirst for over 20 years, and this book is his crowning achievement up to date. It opens as it should with the fundamental aspects of the body fluids, and then goes on to deal with an experimental and theoretical treatment of thirst, drinking, satiety, and dehydration. The approach is physiological and the evidence is not limited to man. The treatment is learned and in many places mathematical, but there is also plenty of writing which even the humblest physiologist or doctor can understand. The whys and wherefores of whether castaways should drink sea-water are dealt with at considerable length, for example. Many quotations are taken from original records, writings, and papers and set out in orderly sequence. This is a very satisfactory way of treating a subject like this and makes the human interest stand out extremely well. After presenting all the available evidence in a most unbiased way the author then leaves the reader to draw his own conclusions. But is this kind? The second part of the book (about 90 pages) consists of a series of transcriptions and articles describing the experiences of people in deserts and elsewhere who have suffered the torments of thirst. The translations from French and other languages are throughout excellent.

An omission from the doctor's point of view is the absence of any treatment of thirst as it affects patients; but the basic facts are there for all to read—and they are easy to interpret. The book cannot be said to be written in basic English, and the author uses a great many strange new words, many of which he must himself have coined. This does not tend to make things easy, but there is a glossary, not to speak of an index and nearly 900 references to previous work. The book is costly, but full of good stuff, and must be given full marks.

R. A. MCCANCE.

PRACTICAL DERMATOLOGY

Roxburgh's Common Skin Diseases. Revised by Peter Borrie, M.A., M.D.Cantab., M.R.C.P.Lond. Eleventh edition. (Pp. 495+xxiii; illustrated. 37s. 6d.) London: H. K. Lewis and Co. Ltd. 1959.

This, the eleventh, is the first edition of this popular textbook since the death of its author, Dr. Roxburgh. It has been revised by one of Dr. Roxburgh's distinguished pupils, Dr. Borrie. Though there have been some alterations and additions to bring the text into line with the advances in dermatology since the war, the pattern remains the same.

The greatest tribute to this book has always been the persistent demand from students which has necessitated so many editions in a relatively short space of time. Among other things, Roxburgh was an enthusiastic photographer, and the book has always reflected his artistic ability in this regard. The standard remains very high, and the illustrations are a valuable part of the work.

Dr. Borrie has partially rewritten the section on syphilis and added information on antibiotics, steroids, and fungous diseases. But in essentials this has always been a simple work dealing with common affections, giving brief, lucid accounts of the outstanding clinical features and omitting the frills which are apt to confuse the student mind. Similarly, treatment is simple and practical and based on personal experience.

There is perhaps a tendency—with the aim of helping the student in his examinations—to present problems in tabular form and to emphasize morphological detail. Provided the practitioner always bears in mind the fact that dermatology is general medicine, this work must be a valuable item in his library.

J. T. INGRAM.

DISEASES OF THE LUNG

Ergebnisse der Gesamten Tuberkulose- und Lungenforschung. Edited by St. Engel, L. Heilmeyer, J. Hein, and E. Uehlinger. Volume XIV. (Pp. 735+viii; illustrated. DM. 144.) Stuttgart: Georg Thieme Verlag. 1958.

This book, Volume XIV of a series covering researches into tuberculosis and other diseases of the lungs, reviews the literature over the last decade, and is designed for the German-reading physician who may not have had access to this extensive literature. The names of Engel, Assman, Beitzke, and Bräuning are among those to be remembered by reason of their original contributions in this field. Volume XIV pays tribute on his 80th birthday to Professor Stefan Engel for his important work on the child's lung, in addition to his outstanding contributions to research in tuberculosis.

Contributions on diseases of the lung from the anatomical, physiological, pathological, radiological, and clinical points of view all find a place in this book. Armstrong and Cudkowicz, writing on the pathological anatomy of the bronchial arteries, summarize original work previously published by them in Great Britain.

The chapter by Schoenmackers and Vieten on studies of selective angiography of the lung is a valuable original contribution and is beautifully illustrated. In addition, there are useful sections on sarcoidosis, the pulmonary fibroses, polyarteritis nodosa, scleroderma, pulmonary haemosiderosis, pulmonary atelectasis in childhood, etc. Tuberculosis as it affects the cardiovascular system, including the heart and pericardium, is well reviewed, as, indeed, are certain diseases of the mediastinum.

Some may question the need for special volumes like this of work already published and to be found in the literature. On the other hand, such a composite picture is valuable for purposes of record. The book is admirably produced, the illustrations are excellent throughout, and the references are comprehensive as well as being international. A few misprints are to be found here and there and the names of authors are not always correctly recorded. Moreover, it is annoying to find that in an index of authors the references do not always correspond with the bibliography relating to each chapter.

PHILIP ELLMAN.

ASTHMA IN CHILDREN

L'Asthme dans l'Enfance. By H. Jumon. (Pp. 120. 900 fr.) Paris: Masson et Cie. 1958.

This small paper-bound book on asthma in childhood discusses the various forms of asthma in children and their causes, and the treatment of attacks. The author recognizes the multiple factors usually concerned in asthma and discusses them fully, but is perhaps more concerned with the tabulation and diagnosis of types and causes than in dealing with the causes themselves. The emphasis would seem to be rather on the treatment, particularly medicinal, of the actual attacks than on any long-term preventive measures. The book does give, however, as comprehensive a picture of asthma in children as is possible within its limited size. It also provides useful suggestions as to medicinal therapy. It is clearly laid out and well printed, and its many subdivisions and headings make reference to any particular section simple. As would be expected from a French publication, spa treatment is given prominence.

C. J. C. BRITTON.

The *Report of Proceedings* of the Eighth Congress of the Universities of the Commonwealth, held in Montreal in September, 1958, is now published by the Association of Universities of the British Commonwealth, 36, Gordon Square, London, W.C.1 (Pp. 100+xxix. 12s. 6d.). One session was devoted to "Medical Education and its Place in the University," and the report includes the opening addresses of Lord Adrian and Dr. F. G. Soper (Otago) to that session. Lord Adrian stressed the value of a university background to medical education. Progress in medical science in the last 20 years had convinced him that the training given had not been so bad, though it needed continual revision to remain useful or even tolerable. He advocated a reduction in factual content of systematic lectures and its replacement by a series of lectures or discussions designed to encourage a critical approach and generally to illustrate the tactical plan of attack, instead of providing the detailed map of the front line. Such lectures would deal with the history and philosophy of medical science, the way modern conceptions have been built up, and the way problems have arisen and been solved or set aside.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Synopsis of Ear, Nose, and Throat Diseases. By Robert E. Ryan, B.S., M.D., M.S.(ALR), F.A.C.S., William C. Thornell, A.B., B.M., M.D., M.S.(ALR), F.A.C.S., and Hans von Leden, M.D., F.A.C.S., F.I.C.S. (Pp. 383; illustrated. 50s.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1959.

Cerebral Angiography in the Management of Head Trauma. By Charles A. Carton, M.D. (Pp. 157+ix; illustrated. 52s. 6d.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Evaluation of Changes Associated with Psychiatric Treatment. By Marvin Reznikoff, M.A., Ph.D., and Laura C. Toomey, M.A. (Pp. 132+xiii. 34s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Intracranial Calcification. By Fermo Mascherpa and Vincenzo Valentino. (Pp. 150+xxi; illustrated. 72s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

The Psychiatric Nurse in the General Hospital. By Mary A. Tudbury, R.N., A.B., M.S. (Pp. 83+xiv. 25s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Synopsis of Ophthalmology. By William H. Havener, B.A. M.D., M.S.(Ophth.). (Pp. 288; illustrated. 50s.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1959.

Diseases of Medical Progress. A Survey of Diseases and Syndromes Unintentionally Induced as the Result of Properly Indicated, Widely-accepted Therapeutic Procedures. By Robert H. Moser, B.S., M.D. (Pp. 131+xvi. 36s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Recreation in Total Rehabilitation. By Josephine L. Rathbone, Ph.D., and Carol Lucas, Ed.D. (Pp. 398+xxiii. 72s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

The Care of Minor Hand Injuries. By Adrian E. Flatt, M.A., M.D., F.R.C.S. (Pp. 266; illustrated. 71s. 6d.) St. Louis: C. V. Mosby Company. London: Henry Kimpton. 1959.

Rheumatic Fever. Epidemiology and Prevention. The Proceedings of a Seminar held at the International Children's Centre, Paris, September 25–27, 1956. Edited by R. Cruickshank, M.D., Ch.B., F.R.C.P., D.P.H., and A. A. Glynn, M.B., B.S., M.R.C.P. (Pp. 193; illustrated. 25s.) Oxford: Blackwell Scientific Publications. 1959.

Nutritional Diagnosis. By Grace A. Goldsmith, B.S., M.D., M.S.(Med.), F.A.C.P. (Pp. 164+xiii. 44s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Soil, Grass and Cancer. Health of animals and men is linked to the mineral balance of the soil. By André Voisin. Translated by Catherine T. M. Herriot and Dr. Henry Kennedy. (Pp. 302+xvii; illustrated. 30s.) London: Crosby Lockwood and Son, Ltd. 1959.

Transactions of the Medical Society of London. Volume LXXV. Edited by Cuthbert E. Dukes, O.B.E., M.Sc., M.D., F.R.C.S. (Pp. 193+lxi.) London: Printed for the Society by F. J. Milner and Sons, Ltd. 1959.

Surgical Service Guide. By Louis T. Palumbo, M.D., M.S., F.A.C.S. (Pp. 208; illustrated. 45s.) Chicago: Year Book Publishers, Inc. London: Interscience Publishers Ltd. 1959.

Bronchial Asthma. A Symposium. Chairmen: J. L. Livingstone, M.D., F.R.C.P., and Sir Geoffrey Marshall, K.C.V.O., C.B.E., F.R.C.P. (Pp. 96; illustrated. 12s. 6d.) London: The Chest and Heart Association. 1959.

Surgical Treatment of Bone and Joint Tuberculosis. By Robert Roaf, M.A., M.Ch.Orth., F.R.C.S.Ed., F.R.C.S.Eng., W. H. Kirkaldy-Willis, M.A., M.D., B.Chir., F.R.C.S.Ed., and A. J. M. Cathro, M.B., Ch.B. Illustrated by W. Cannell, M.C.S.P. (Pp. 137+viii. 30s.) Edinburgh and London: E. and S. Livingstone Ltd. 1959.

Arterial Embolism in the Limbs. The Clinical Problem and its Anatomical Basis. By A. L. Jacobs, M.A., D.M.(Oxon.), F.R.C.P. (Pp. 200+xii; illustrated. 35s.) Edinburgh and London: E. and S. Livingstone Ltd. 1959.

BRITISH MEDICAL JOURNAL
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TESTING ADRENOCORTICAL FUNCTION

The adrenal cortex secretes a number of physiologically active steroid hormones, including oestrogens, androgens, and progestogens. But the uniquely vital functions of the gland come from two hormones, cortisol and aldosterone, which are the natural prototypes of the gluco-corticoid and mineralocorticoid steroids. The accuracy with which adrenal hormones and their metabolites can be detected in the body fluids not only concerns the diagnosis of primary disorders of the gland ; it also sets limits of precision for research into such problems as the after-effects of treatment with corticosteroids and corticotrophin, the control of hormone-dependent cancer, and the causes and management of oedema, to name a few.

Not long ago the diagnosis of adrenal disease depended on a bedside assessment of the case supported by histological and simple biochemical tests. The diagnostic path, except in the more florid cases, was strewn with notorious pitfalls. Correlation between adrenal function and histological appearances was poor, and there was little understanding of the diversity of these functions in relation to the various secretions of the gland. Aldosterone had yet to be isolated, and little was known about adrenal oestrogens and androgens. Indirect tests of adrenal function based on the patient's ability to excrete a water load or on eosinophil counts lacked quantitative value, though useful for screening cases.

The ability to measure adrenal function came only with the means of estimating adrenal hormones and their metabolites in urine. The first group of steroids to be assessed on a routine scale were the urinary total 17-ketosteroids. This mixture of adrenal and testicular waste-products provided few qualitative data, though sometimes useful information can be got from measuring the individual components ; but this requires chromatographic separation and is hardly feasible for routine use. The output of 17-ketosteroids is often low in debilitating conditions without implying any failure of the vital adrenal secretions. High levels of output are usually associated with androgenic effects and can occur when secretion of cortisol and aldosterone is diminished, as in some cases of the adrenogenital syndrome. Often in Cushing's syndrome due to adrenal hyperplasia the output of 17-ketosteroids is normal.

Considerable technical difficulties have beset the isolation of aldosterone and cortisol from urine. But, from crude beginnings, progressive refinements of method have now reached the stage at which these hormones can be measured in body fluids in terms of a few microgrammes per 100 ml. ; and by using radioactive isotopes of adrenal hormones it is possible to estimate their actual rate of secretion with a fair degree of accuracy.[1–3] Technical difficulties make the estimation of aldosterone still a research procedure. It has yielded a rich harvest of information, some fruits of which were discussed recently in these columns.[4]

The rate of secretion of cortisol is roughly mirrored by the urinary output of 17-ketogenic steroids,[5] and this estimation has become a standard laboratory procedure. It is far from specific, for the group includes other steroids with a 17-hydroxyl group, such as compound S and pregnanetriol ; but usually these are present only in small amounts. The rate of output of 17-ketogenic steroids is used not only to indicate the resting level of the glucocorticoid secretion but to test the response of the gland or its tumours to stimulation by A.C.T.H. or suppression by synthetic analogues of cortisol, such as 9-alpha-fluorocortisol. This additional information is of diagnostic value in primary adrenal disease and in studying the effects on the gland of prolonged treatment with corticosteroids and A.C.T.H. Much information has now accrued relating the output of 17-ketogenic steroids to various adrenal disorders, and the time is ripe to take stock of its reliability as an index of cortisol secretion.

In the opening pages of the *Journal* this week an important communication by Dr. C. L. Cope and Mr. E. G. Black is devoted to this problem. Their conclusions are derived from comparing the urinary excretion of cortisol, cortisone, and their two tetrahydro-metabolites with that of 17-ketogenic steroids in patients with Cushing's syndrome, before and after adrenal function had been suppressed by 9-alpha-fluorocortisol. In Cushing's syndrome the output of 17-ketogenic steroids is usually much increased, but may lie within the upper range of

[1] Ayres, P. J., Garrod, O., Tait, S. A. S., Tait, J. F., Walker, G., and Pearlman, W. H., *Ciba Found. Colloq. Endocrin.*, 1957, **11**, 309.
[2] Peterson, R. E., and Wyngaarden, J. B., *J. clin. Invest.*, 1956, **35**, 552.
[3] Cope, C. L., and Black, E. G., *Clin. Sci.*, 1958, **17**, 147.
[4] *Brit. med. J.*, 1959, **2**, 553.
[5] Norymberski, J. K., Stubbs, R. D., and West, H. F., *Lancet*, 1953, **1**, 1276.
[6] *Brit. med. J.*, 1959, **2**, 148.

normal. Cope and Black find that the urinary output of cortisol is twice as sensitive an index of hyperadrenalism as that of the 17-ketogenic steroids, and gives a much smaller overlap between normal and abnormal. The explanation for this difference probably lies in the degree of protein-binding of cortisol to transcortin[6] in the plasma ; for this binding is less at high than at low concentrations of the hormone, leaving a much greater proportion of freely diffusible cortisol available for renal filtration.

When 9-alpha-fluorocortisol is used to suppress adrenal function in Cushing's syndrome, the reduction in urinary output of cortisol is many times greater than that of 17-ketogenic steroids. This again seems to be partly an effect of protein-binding, for the amount of diffusible cortisol in plasma falls much more rapidly than the total hormone.

Cope and Black have also estimated the rate of secretion of cortisol in their cases, using radioactive cortisol.[3] This has provided a check on the accuracy, as indices of adrenal function, of the urinary outputs of cortisol and 17-ketogenic steroids. Paradoxically, the urinary cortisol was more sensitive in indicating, and indeed showing in exaggerated form, changes in the rate of secretion of cortisol, but the output of 17-ketogenic steroids correlated more closely with the rate of secretion. The explanation probably lies in how cortisol is bound in plasma. These conclusions are valid only for high levels of adrenal activity ; within the normal range there was very little correlation between the output of either cortisol or 17-ketogenic steroids and the rate of hormone secretion.

Owing to the very small amounts excreted, the urinary cortisol is not a sensitive index of adrenal hypofunction. But the tetrahydro-metabolites of cortisol and cortisone are put out in much larger quantities, and can be measured at 5% of their normal mean output. There is a difficulty in assessing incomplete degrees of adrenal failure because a small remnant of adrenal tissue may be working under maximal stimulation to secrete quantities of hormone which are just within the normal range but insufficient to protect against the effects of major stress. This situation can be revealed by showing a failure of response to stimulation by A.C.T.H. The urinary 17-ketogenic steroids are a sensitive enough index for this purpose.

For general clinical purposes it must be concluded that the 17-ketogenic steroids provide the best available test of adrenal glucocorticoid secretion. But the test has severe limitations, particularly when applied to borderline cases of adrenal dysfunction. For accurate diagnosis of these cases, and for purposes of research, there is need for more precise methods, and the most promising seem to be those which measure by radio-isotope techniques[2 3] the actual rate of cortisol production.

TREMOR AND STABILITY

As a necessary condition of life in a constantly changing environment the human body must preserve some sort of internal stability.[1] Yet the self-correcting properties of many nervous reflexes have until recently received little attention. For example, the pupillary response to light[2] keeps the intensity of stimulation to the retina within limits ; the stretch reflex[3] helps to preserve the length of a muscle constant against different external loads.

As W. B. Cannon suspected,[1] there are general principles underlying the behaviour of such systems, and they extend beyond the realm of biology. Automation in industry has entailed the invention of many types of electrical and mechanical self-correcting systems such as the automatic pilot and the automatic rudder. Mathematicians have formulated general laws,[4] and biologists are trying to see how far these laws apply to their own more complex systems. Self-correcting devices are often apt to overshoot the correct position and then embark on a series of oscillations. For instance, the time-lag between receiving the stimulus and correcting the temperature of the environment causes simple thermostats to keep the temperature oscillating within certain limits. Oscillations may even build up to the point of catastrophe, as an inexperienced helmsman may find if he is overzealous in his corrections. There now seems to be fairly strong evidence for regarding physiological tremor as an oscillation due to the time-lag in the self-correcting system of the stretch reflex. This has come to be known as the " servo-loop " hypothesis of tremor.

Physiological tremor is not a matter of perfectly regular sine waves. Several workers have analysed the actual frequency components.[5-9] As E. A.

1 Cannon, W. B., *The Wisdom of the Body*, 1932, London.
2 Stark, L., and Sherman, P. M., *J. Neurophysiol.*, 1957, **20**, 17.
3 Hammond, P. H., Merton, P. A., and Sutton, G. G., *Brit. med. Bull.*, 1956, **12**, 214.
4 Wiener, N., *Cybernetics*, 1948, New York.
5 Sutton, G. G., *Quart. J. exp. Psychol.*, 1957, **9**, 42.
6 Halliday, A. M., and Redfearn, J. W. T., *J. Physiol.* (*Lond.*), 1956, **134**, 600.
7 Redfearn, J. W. T., *J. Neurol. Neurosurg. Psychiat.*, 1957, **20**, 302.
8 Lippold, O. C. J., Redfearn, J. W. T., and Vuco, J., *J. Physiol.* (*Lond.*), 1959, **146**, 1.
9 —— —— —— ibid., 1957, **137**, 473.
10 Schäfer, E. A., Canney, H. E. L., and Tunstall, J. O., ibid., 1886, **7**, 111.
11 Lippold, O. C. J., Redfearn, J. W. T., and Vuco, J., ibid., 1957, **138**, 14P.
12 Lazarus, S., and Bell, G. H., *Glasg. med. J.*, 1943, **140**, 77.
13 Marshall, J., and Walsh, E. G., *J. Neurol. Neurosurg. Psychiat.*, 1956, **19**, 260.
14 Halliday, A. M., and Redfearn, J. W. T., ibid., 1958, **21**, 101.
15 Lippold, O. C. J., Redfearn, J. W. T., and Vuco, J., *J. Physiol.* (*Lond.*), 1958, **144**, 373.
16 Birzis, L., and Hemingway, A., *J. Neurophysiol.*, 1956, **19**, 37.
17 Denny-Brown, D., *Proc. roy. Soc. B.*, 1928, **103**, 321.
18 Granit, R., *J. Neurophysiol.*, 1950, **13**, 351.
19 Marshall, J., *J. Neurol. Neurosurg. Psychiat.*, 1959, **22**, 33.

Schäfer and colleagues[10] and subsequent authors have affirmed, there is usually a rhythmical component of about 10 cycles per second. But there is also an irregular component containing all frequencies up to 20 or 30 cycles per second. The state of affairs is analogous with a pure note heard more or less intermittently against a background of noise. The same frequency distribution (with greater amplitudes) has been found by O. C. J. Lippold, J. W. T. Redfearn, and J. Vuco to characterize human shivering due to cold[8] and the tremors of emotion and of muscular fatigue.[11] Thyrotoxic tremor probably has the same frequency characteristics.[8 12] A similar range of frequencies is found in the muscles of cats, whether the activity is produced by cortical stimulation, shivering, or reflex stimulation.[8] In the cat the frequency of the regular component is about 15 per second.

The servo-loop hypothesis concerns the rhythmical component, which Lippold and colleagues[9] have shown to be due to rhythmical bursts of action potentials in the nerves to the muscles. This fact, and the fact that the isolated nerve–muscle preparation shows no predilection for the normal frequency when stimulated at various frequencies,[11] refute the hypothesis[13] that the rhythm is due to the properties of muscular contraction. Yet, with the muscle cooled, the rhythm slows down[9] *pari passu* with the prolongation of the twitch time of the muscle. From these findings taken together, Lippold, Redfearn, and Vuco argue that the slowing effect of local cooling must be acting via the stretch reflex. They have recently provided further evidence for the servo-loop theory by showing that section of dorsal roots in the cat abolishes the regular but not the irregular components of shivering. A. M. Halliday and Redfearn[14] had previously shown that, in tabetic patients, the regular component is absent in those muscles with severe loss of afferent nerves, whereas the irregular component may be greatly increased. These observations on muscle that is cooled or lacking in afferent nerves, as well as more indirect evidence obtained from the rhythmical stretching of muscle,[15] seem to rule out the possibility that the rhythm is due to a spinal pacemaker or to higher centres. But it is certain that higher centres, notably the hypothalamus,[16] can control the amplitude of the oscillations, which vary with emotion and with the state of attention.[8]

In oscillating servo-mechanisms the period of oscillation is twice the time interval between a stimulus and the correcting response. In the case of the stretch-reflex mechanism, the total delay around the loop includes the time taken for the muscle to lengthen under the influence of the external load, the time for this stretching to activate the muscle spindles, the conduction times to and from the spinal cord, plus the duration of synaptic delay, and the time taken for the motor impulse to generate action potentials in muscle fibres and then cause muscular contraction. In other words, the delay in the loop depends not only on the conduction time round the nervous pathways but also on the twitch speed of the muscle and the sensitivity of the muscle spindles. The importance of these latter variables is shown by the fact that cooling muscles in cold tap-water slows the rhythm to 6 per second without altering the reflex time.[9] In clonus, which is another type of self-maintaining oscillation of the stretch reflex, with a frequency about 6 per second, the period seems to be lengthened by a spinal inhibitory process[17] probably originating in tendon organs[18] stimulated by the contracting muscle.

J. Marshall[19] has recently shown that physiological tremor has a predominant frequency of 6 per second in children. He has pointed out that reflex delay is probably shorter in children than in adults because of shorter pathways and that a simple servo-loop hypothesis might lead to the expectation of a faster rather than a slower rhythm. He does not discuss the possibilities of slowing due to a clonic element or to slower muscle action, which might perhaps account for his findings. The faster rhythm might be present in children even if not predominant. Redfearn[7] has shown that in cases of severe neurotic tremor a slow component may appear in addition to the normal rhythm, and this may correspond to the clonic tendencies to be seen clinically in these patients. Marshall's work does, however, indicate that a distinct mechanism may be operating in children. It is just possible that tremor in childhood may be completely distinct from adult physiological tremor, just as Parkinsonian tremor is, but further evidence is needed.

Another problem lies in the cause of the irregular component of tremor. Lippold, Redfearn, and Vuco[8] point out that this must be due to a tendency towards synchronous firing by the motoneurones. This can be increased by damage to motoneurones, as in tremor due to mercury poisoning or poliomyelitis. What produces such an increase in the irregular component in shivering, emotion, and thyrotoxicosis is still debatable. It can be hoped that frequency analysis and a combination of human and animal experimentation will continue to provide answers to these problems.

"H3"

No one would deny that procaine is an interesting compound about which there is much still to be learned. It has been used as a local anaesthetic under the brand name of "novocain" for over 50 years. There seems no excuse for now giving it a new and meaningless name and "promoting" it to the status of a vitamin, which it most certainly is not. For H3 is simply procaine,[1] and the popularization of procaine under this description in a section of the lay press has confused many people, as witness the recent heart-cry of a doctor in this *Journal*[2] who, not realizing that he could buy it over the counter from the nearest pharmacist, found great difficulty in importing it from Bucharest. It has also led to an unethical attempt at commercialization, which we hope will be unsuccessful, within the ranks of the medical profession.

The uses of procaine, apart from its oldest and most frequent one as a local anaesthetic, have been many, and much is known of its activity. It is diethylaminoethyl-*p*-aminobenzoate. It belongs to the alkamine ester group of compounds, all members of which possess, in varying proportions, activities similar to atropine, quinidine, and curare, and are anticholinergic, antihistaminic, and anaesthetic. In virtue of these properties it has been injected intravenously to control cardiac arrhythmias, to provide fields of operation unobscured by blood, to give general analgesia without unconsciousness during the dressing of burns, to relieve post-operative pain, to increase the vital capacity and so to reduce the incidence of pulmonary complications after abdominal surgery, to relieve pruritus, urticaria, and status asthmaticus, and to improve the circulation in many vascular diseases such as coronary disease, pulmonary embolism, Buerger's disease, intermittent claudication, and incipient gangrene. It has been found useful in many allergic states and in anuria, and to relieve muscle spasm. Though in many of these conditions it has been superseded by more potent or more convenient remedies, its use in all of them was founded on its known properties. Perhaps one of its most valuable uses, overshadowed in the last 10 years by that of corticotrophin and the corticosteroids, was in the treatment of rheumatoid arthritis, in which, somewhat mysteriously, relief often outlasted any possible local anaesthetic effect or the time taken for hydrolysis to occur.

Procaine is broken down in a few minutes by procaine esterase in the plasma and to a lesser extent by a hepatic enzyme. The products are *para*-aminobenzoic acid and diethylamino-ethanol, neither of which has the properties of procaine. Its rapid breakdown makes it a very safe drug in expert hands. Even in large doses it is completely eliminated from the blood-stream in 20 minutes. Doses as high as 10 g. a day have been given in slow intravenous infusions. If the optimal dose is exceeded, the signs of overdosage are pins-and-needles, dizziness, twitching, convulsions, and ultimately loss of consciousness. Vitamin-C deficiency increases the liability to such side-effects, and barbiturates reduce it. Procaine must never be given in combination with neostigmine, which retards its breakdown.

In a series of papers since 1956 Professor Anna Aslan and her colleagues at the Parhon Institute of Geriatrics, in Bucharest, have advocated the use of procaine in a much wider group of disorders, including senility.[3-6] They have confirmed the observations of previous workers in the treatment of arthritis, trophic disturbances, vasospasm, and asthma. But at the same time they claim to have benefited, both in experimental animals and in man, the nutritional state, the quality and colour of skin and hair, and, in senile patients, a variety of mental processes, muscular tone and strength, the activity of the endocrine glands, and the peripheral circulation. According to these workers blood pressure was reduced and cardiac ischaemia improved, appetite improved, peptic ulcers healed; cerebral arteriosclerosis, Parkinson's disease, and deafness were improved. A true rejuvenation is claimed.

The method used by Professor Aslan consists in the injection of 5 ml. of a 2% solution of procaine at a *p*H between 4.2 and 5.0. This very small dose is given three times a week in series of 12 injections with 10-day intervals between. Since it takes only a few minutes for a dose of procaine to be completely hydrolysed to *para*-aminobenzoic acid and diethylaminoethanol, it is difficult to understand the system of dosage, especially as Professor Aslan admits that similar results cannot be obtained by the breakdown products of procaine. It would appear that any good results, other than local anaesthesia, are likely to be obtained only by continuous infusion over a prolonged period. Incidentally, in most of these papers the drug is referred to under its former and familiar proprietary name of "novocain." The magic number "H3" was introduced "in order to emphasize the role of novocain as a biocatalyst and to differentiate it clearly from *para*-aminobenzoic acid H1 and H2."[3]

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1 *Brit. med. J.*, 1959, 1, 872.
2 Ibid., 1959, 1, 1360.
3 Aslan, A., *et al.*, "*Research on Novocain Therapy in Old Age*," being the English translation of seven papers from *Die Therapiewoch*, 1956-7, Consultants Bureau Inc., 1959.
4 —— *Ther. Umsch.*, 1956, 13, 165.
5 —— *Med. Klin.*, 1957, 52, 1760.
6 Parhon, C. I., and Aslan, A., *Rev. Sci. méd. (Bucuresti)*, 1957, No. 2, 5.

A study of the clinical reports of the Parhon group makes sad reading for the clinician trained in modern scientific method. There is an almost complete absence of controls, and blind trials were never used. At two meetings held at the Apothecaries' Hall last week (one of which is reported at p. 1175), Professor Aslan created a most favourable personal impression as a woman gifted with humour, charm, enthusiasm, and (here was the rub) boundless therapeutic optimism. But two questions aimed at elucidating the plan of her experiments and her statistical methods were deftly turned aside. The word "statistical" was heard frequently, but no worthwhile statistics were shown. The audiences heard little but a series of medical anecdotes.

One question was concerned with the value of a sorry piece of commercial polypharmacy, consisting of a mixture of procaine and vitamins. Professor Aslan briskly replied that her name had been used by the makers without her permission and that she knew nothing of the substance. "It may be good. I don't know." The same may be said of procaine alone as a rejuvenating drug. There is no real evidence that it is any good at all, and the extensive publicity given to it in the Press will have the unfortunate effect of raising the hopes of many that at long last the elixir of life has been discovered. The search for this, for the philosopher's stone, for the panacea, makes a fascinating chapter in the history of healing; and has always turned out to be the dream-child of the alchemist.

REGISTERING MEDICAL AUXILIARIES

A Bill,[1] published last week, names eight new bodies for registering members of certain "professions supplementary to medicine" and with the general task of promoting high standards of education and conduct among them. Those concerned are chiropodists, dietitians, medical laboratory technicians, occupational therapists, physiotherapists, radiographers, remedial gymnasts, and speech therapists. The specific duties of these boards will be to maintain a register of qualified persons, to approve training courses and supervise approved training institutions, and to remove from the register the names of those guilty of misconduct. Over the boards there is to be a co-ordinating council with more than merely nominal powers of supervision: it is expected to make proposals to the boards about their activities and may limit these in "such manner as the council considers appropriate after consultation with the board." The recommendations of both boards and council on the acceptance of training courses and qualifications will need the approval of the Privy Council.

The council will have 23 members, of whom eight will be medical practitioners (two appointed by Ministers, three by the English Royal Colleges, two by the Scottish Corporations, and one by the General Medical Council) and eight will be representative members of the registered professions (one appointed by each of the boards from among the members of the board representative of the registered professions). The boards will have varying numbers of members, but in each the representatives of the professions concerned—who, after the first appointments, will be elected—will be in a majority of one. The remaining members will include medical practitioners nominated by professional bodies (including in two instances by the B.M.A. and in three by the Society of Medical Officers of Health) and experts in professional education.

The decision at last to bring those previously known by the honourable title of medical auxiliaries into line with the others in the National Health Service will give satisfaction to those who have long wished to see them given statutory recognition. The Government's failure to give effect to the Cope Committee's recommendations,[2] because there was insufficient agreement on fundamental matters "to proceed with statutory registration," caused disappointment at the time.[3] Since then discussions have dragged on in an effort to find common ground in the different opinions held by persons in the various vocations gathered under the title of medical auxiliary.

A contentious matter was the medical profession's insistence on a predominance of doctors on the registering bodies. The composition of the boards and council proposed in the Bill shows that the medical view has not been conceded. This has not resulted from the Minister's ignorance of it. As recently as last March he heard the authoritative opinion of the Joint Consultants Committee, and of representatives of those specialist medical associations most closely connected with the work of auxiliaries. Reports in the *Supplement* of meetings of the B.M.A.'s Central Consultants and Specialists Committee show that this committee feels strongly on the matter, and the A.R.M. has endorsed its view.

[1] Professions Supplementary to Medicine Bill, 1959. H.M.S.O., London. Price 1s. 6d. net.
[2] *Brit. med. J.*, 1951, **1**, 869 and 877.
[3] Ibid., 1953, **1**, 1267.

The medical profession is right to claim that professions supplementary to it should remain under its wing, because the ultimate responsibility for treatment must lie with the doctor. There is a danger in attempts to foster independence among those who work with but under him, and this danger is not least to those who would wish to be independent. What the public needs is a guarantee that medical auxiliaries are adequately trained in their work and that they should have the status that goes with registration. What better guarantee of this could there be than that the registering bodies should be predominantly medical in composition ?

GRISEOFULVIN

Griseofulvin is an antibiotic against fungi. It was isolated from a number of *Penicillium* species twenty years ago by A. E. Oxford and colleagues[1] and has been used in horticulture as a local application in the treatment of moulds attacking lettuce and glasshouse vegetables. Its use in animals was considered some years ago but rejected because griseofulvin was shown to be a mitotic poison when injected intravenously. More recently J. C. Gentles[2] found it to be effective in curing dermatophyte ringworm infections in animals when given by mouth, and this experimental work has been carried into human practice.[3]

It appears to be effective against all dermatophyte ringworm infections but not against candidiasis or aspergillosis, actinomycosis, or madura foot. The drug has an affinity for keratin, where it exercises its effect on the fungal mycelium, the "curling effect." It has to be taken, it appears, until all infected keratin has been shed, since griseofulvin is only fungistatic and not fungicidal. Infection of toe-nails may require as long as twelve months' treatment. The antibiotic is not effective when applied topically, only when taken by mouth. Dosage has been about 250 mg. four times a day for adults and half that for children, but this may be found to be in excess of requirements.

Successful treatment in man has been reported from many parts of the world without serious toxic effects. Nevertheless, the drug is a potential mitotic poison, as shown by G. E. Paget and A. L. Walpole,[4] when injected intravenously into animals in large doses, and care is obviously called for in using it to treat a benign infection. Depression of the absolute polymorph count is not uncommon while patients are under treatment, though recovery has been rapid on stopping the griseofulvin. This is confirmed by Dr. A. J. E. Barlow and colleagues in their article at p. 1141 of the *Journal* this week. It is clearly wise as yet to keep patients under close clinical observation and to watch the blood picture during treatment. There is occasional evidence of gastric intolerance, which can sometimes be overcome by the simultaneous administration of an antihistamine. In the main, the administration of griseofulvin should be restricted to the treatment of incurable fungous infections such as *Microsporum audouini* and *Trichophyton rubrum*, and mycological investigation, with culture of the fungus, should first be undertaken. Severe pustular reactions from cattle ringworm, kerion lesions, sometimes take months to heal, and this course can be reduced to weeks by the use of griseofulvin. The drug should not be used indiscriminately, especially for ringworm of the feet, where the diagnosis is often difficult or impossible to make without investigation. It is not generally appreciated that the clinical picture of "athlete's foot" is commonly produced by a variety of causes other than ringworm fungus ; they include bacteria, *Candida albicans*, eczema, and sweating.

In an article at p. 1137 of the *Journal* Drs. M. Beare and D. Mackenzie report persistence of viable fungus in hairs after apparent clinical cure and disappearance of fluorescence under Wood's light. They did not employ any local fungicidal measures, which may account for their findings, but it is a matter that must receive attention. They found that no fresh lesions appeared in patients under treatment, and suggest that it may be of value in protecting contacts. They found griseofulvin to be non-toxic to children, but it would seem early days to suggest the use of a potentially toxic drug in healthy children as a prophylactic measure, and unnecessary. Even so, this drug marks a revolutionary advance in the oral treatment of ringworm infections.

[1] Oxford, A. E., Raistrick, H., and Simonart, P., *Biochem. J.*, 1939, **33**, 240.
[2] Gentles, J. C., *Nature* (*Lond.*), 1958, **182**, 476.
[3] Williams, D. I., Marten, R. H., and Sarkany, I., *Lancet*, 1958, **2**, 1212.
[4] Paget, G. E., and Walpole, A. L., *Nature* (*Lond.*), 1958, **182**, 1320.

NEW INDUSTRIAL HAZARDS

New materials and new processes in industry can mean new risks to health. Last week the second report of a committee concerned with health and welfare in non-ferrous foundries appeared.[1] It includes a special part prepared by Dr. W. D. Buchanan, and covers potential as well as known risks, for the committee considers that "a good knowledge of this part would result in the avoidance of many risks which might otherwise be introduced inadvertently with new processes."

The committee reports that pneumoconiosis is not, as had been thought until recently, of negligible incidence in non-ferrous foundries as compared with iron and steel foundries. This low incidence has been partly maintained by the prohibition in 1950 of the use of silicious parting powders, but in 1953–6 at least 27 non-ferrous foundry-workers have been accepted for pneumoconiosis medical benefit, and between 1945 and 1956 14 deaths occurred in which pneumoconiosis was recorded as a cause. It is not possible to say how great a part was played in these cases by past working

[1] *Second Report of the Joint Standing Committee on Safety, Health, and Welfare Conditions in Non-ferrous Foundries*, 1959. H.M.S.O., London. 1s. 9d.

conditions, but the records point to the possibility of this hazard in non-ferrous foundries. Metal-fume fever in brass foundries, for which zinc is the metal chiefly responsible, is much less common than formerly, almost certainly as the result of improved ventilation in casting. Lead poisoning is a possibility when fumes of molten lead or lead-rich alloys are the source of exposure. Blood examinations in four foundries, while revealing no significant degree of anaemia, did suggest slight absorption of lead.

Fumes other than those considered in the committee's first report in 1957 include beryllium, cadmium, magnesium, phosphorus, selenium, tellurium, and vanadium. Beryllium has so far caused no cases of poisoning in Great Britain, but records from the U.S.A. give serious warning of the high risk of both acute and chronic beryllium disease wherever its fumes or dust are produced, and of the considerably higher standard of control required to prevent it than that for the commoner toxic dusts and fumes. Cadmium has caused a chronic lung disease, differing from chronic bronchitis but causing disability, and it has been added to the list of prescribed diseases for which industrial injuries benefit is payable. Magnesium fume has not yet been shown clearly to have a harmful effect, but magnesium castings may be etched by boiling in sodium bichromate solution, and the bichromates are a potent source of irritation and ulceration of the skin and mucous membranes, especially of the nose. Phosphorus is normally handled as a master alloy with copper, in which form there is no risk of poisoning, but occasionally yellow phosphorus, which is highly poisonous, is added in direct stick form, and molten splashes may cause severe burns. Selenium and tellurium are as metals relatively non-toxic, but their compounds, especially the fumes caused by oxidation of tellurium, may cause nasal and throat irritation and a most unpleasant garlic-like odour of the breath. Vanadium has caused respiratory disorder from contact with ores containing it and from the cleaning of oil-fired boilers.

Many fluxing and degassing agents produce fumes irritating to the lungs. Fluorine fluxes have caused bone changes in processes where exposure is more severe than that to be expected in the average foundry, and care is necessary in handling them. The carbon dioxide process used in the coating of moulds and cores carries certain risks from the organic solvents used, and from the formation of sodium carbonate and synthetic silica during the reaction, but no definite opinion on the hazard arising from dust in this technique is expressed. In shell moulding, dermatitis from resin powder is, in the absence of stringent precautions, the most probable ill effect; there has not yet been time to assess the potential risk of pneumoconiosis from exposure to the fine silica sand.

First-aid treatment is of special importance in the treatment of burns from molten metal, which form a large proportion of all foundry accidents. Where the only facilities are boxes in charge of first-aid workers, it is essential that the latter should be specially trained to deal with these burns. The method of treatment advised is application of dry, sterilized dressings to the injured area, first-aid treatment for pain and shock, and rapid transfer of the patient to hospital. Finally, the committee agrees that medical supervision is desirable wherever it can be arranged, and it recommends a general medical survey of the industry to establish the kind and magnitude of the health risks in it.

HOSPITAL COSTS

Just over a year ago[1] we drew attention to the results of the first year of the new hospital costing system. For about 250 hospitals, most of them acute or mainly acute, and each of them spending £150,000 or more a year, this system has replaced the old, simpler costing returns, which analysed hospital expenditure under subject-headings—salaries and wages, provisions, fuel, drugs and dressings, etc.—deducted the estimated cost of out-patients by means of a formula, and then purported to give the weekly cost of treating an in-patient.

The old analysis, for all its defects, provoked interesting speculations about why comparable hospitals could differ so much in their costs. In their new form the returns show where these differences in costs arise, but they do not show why they arise. For instance, a year ago St. George's Hospital had achieved the position of being the most expensive of the undergraduate teaching hospitals, largely, it appeared from the new costing returns, because of a particularly heavy bill for works and maintenance. In the latest returns,[2] covering the year ended March 31, 1959, its figure for this item has fallen, and St. Thomas's is again "head of the river" with a net in-patient cost per week of £38 17s., compared with an average for the London teaching hospitals of £34 13s. 6d., and with the provincial teaching hospitals' average of £29 9s. 2d. The figure for the London Hospital is £31 2s. 11d. a week. Rather more than £3 a week of the difference between the London in-patient cost and that of St. Thomas's Hospital can be explained by higher expenditure at St. Thomas's on salaries and wages, and about £4 by its higher indirect expenditure on such items as general administration, catering, works, power, lighting, heating, and so on.

The average cost per in-patient week in the non-teaching acute hospitals rose from £22 6s. 2d. in 1957–8 to £23 14s. 5d. in 1958–9. Over half of this increase, 16s., is accounted for by higher expenditure on the salaries and wages of doctors, nurses, and domestic staff (1s. 4d., 7s. 5d., and 7s. 3d. respectively), and 4s. 2d. by the higher cost of catering. It is also worth noting that the national average of £23 14s. 5d. conceals some big regional differences. The Liverpool region's average, for instance, was only £19 14s. 1d., whereas both the South-western Region and Oxford had averages of over £27.

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[1] *Brit. med. J.*, 1958, 2, 1153.

[2] *National Health Service Hospital Costing Returns, Year Ended March 31, 1959*, vol. 1, 1959. H.M.S.O., 35s.

Drug Treatment of Disease

DRUGS IN THE TREATMENT OF SEBORRHOEA

BY

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Literally the term seborrhoea means a running of sebum, but here it is used to indicate the wide range of dermatoses related to and dependent upon the seborrhoeic diathesis. It must be said that such terminology, or indeed the idea of such a diathesis, is by no means universally accepted, but it has had an established place in British dermatology since Unna propounded his views on seborrhoeic dermatitis and the skin organisms involved.

Distribution of eruption and age of patient rather than a greasy skin often determine the label seborrhoeic, the distribution being that in which sebaceous glands and to some extent sweat glands are most in evidence—scalp, face, mid-trunk, and flexures. The age factors again relate to phases of major activity of such secretory glands at puberty and adolescence, menopause, and sometimes old age. Such activity may, however, be affected by other considerations such as climate, occupation, and systemic disease, including febrile, endocrine, and central nervous disorders.

Some would, as I think correctly, regard the diathesis as affecting the whole patient and not merely the skin, but chief attention will be paid here to the skin, though general considerations cannot be entirely excluded (Ingram, 1957).

Epidermal Hypertrophy

Characteristically the skin of the seborrhoeic patient is more greasy and coarse from increased size and activity of sebaceous glands and epidermal hypertrophy. There is usually increased sweating, especially in axillae, hands, and feet, and there may be a flabbiness from increased water content of the tissues. These changes may determine a plugging of follicles with horn and inspissated sebum, and in adult life may be associated with epidermal tumours, the benign so-called seborrhoeic warts and tags which have no tendency to malignant change.

The altered functional state of the seborrhoeic skin, and especially the change in the mantle of secretion and the water balance of the tissues, affects the normal resident flora of the skin but also increases its susceptibility to transient pyogenic infections, and increases its sensitiveness to external irritants; indeed, it renders the skin eczema-prone. The mantle of secretion on the skin consists of fats and waxes from disintegrating horn cells, the secretion of the holocrine sebaceous glands, and the eccrine sweat and apocrine glands. The sweat particularly serves to emulsify the whole and spread it over the surface.

Hormonal Balance

The *p*H and the relative proportion of the constituents vary with the state of health and particularly with hormonal balance and with emotional tone, the latter often being intimately confused with the endocrine as at puberty, adolescence, and menopause. The apocrine glands come into functional activity only at puberty, and they cease to function with the menopause. The span of sexual activity has a distinct influence upon the function of the other secretory glands. The increased secretion of certain saturated fatty acids, for instance, tends spontaneously to cure microsporum infection of the scalp hair in children at puberty (Rothman, 1954).

The increased sebaceous secretion, especially at puberty, is usually more acid than normal, though increased sweating may be associated with alkalinity. Beare *et al.* (1958) have found recently that newborn babies showing seborrhoeic manifestations tend to have a more alkaline skin, but here the position may be complicated by the fact that the normal child before puberty does not show seborrhoeic features because of endocrine immaturity, and in the baby the effects are probably dependent upon hormonal factors derived from the mother. From all this it will be clear that endocrine function associated with sexual maturity plays an important role in the aetiology of the seborrhoeic state and its disorders, but in spite of much clinical and experimental evidence of the relationship there is not yet any clear-cut therapeutic answer to the problems as there is in the administration of thyroid for myxoedema.

It must further be emphasized that not all the skin changes mentioned will necessarily be seen in all dermatoses that are labelled seborrhoeic because of their clinical character and distribution.

Seborrhoeic dermatoses tend to be of a chronic or long-term character and only limited success can be achieved by local treatment. It is for this reason that attention is drawn to the systemic aspects of such disease, even though local treatment is of importance and will be dealt with first.

The dermatoses that will be considered are seborrhoeic pityriasis capitis and corporis, infective seborrhoeic dermatitis and sycosis, and rosacea.

The ordinary eczematous dermatitis and ordinary pyoderma in the seborrhoeic will not be discussed here.

Pityriasis Capitis and Corporis

In lay terms this concerns scurf of scalp, or dandruff, and "flannel rash" of mid-chest and back. These are associated with abundant growth of the normal skin organisms, particularly the *Pityrosporum ovale* ("bottle bacillus") and diphtheroids. Any mild antiseptic measures are curative, but vigorous or strong measures may provoke an eczematous dermatitis. The old-fashioned mercurial (2% hydrarg. ammon.) and sulphur-and-salicylic (2%) ointments, together with the use of soap and water, are rapidly effective. Flannel and wool—which are not boiled and sterilized—should not be worn next the skin.

On the scalp a mercurial and resorcin lotion as in the following prescription is effective, but a suitable weekly

shampoo is necessary; one incorporating 15% cetrimide and 15% lanolin is recommended. The popular selenium sulphide preparations (like the old-fashioned mercurial cinnabar) are also good but carry the risk of irritation and sensitization and even falling of hair if used too frequently.

Hydrarg. perchlor.	...	...	2 gr. (0.13 g.).
Tinct. cantharid.	...	...	1 dr. (3.5 ml.).
Indust. spirit	...	...	2 oz. (57 ml.).
Resorcin ...	...	...	1 dr. (4 g.).
Aq. dest. ...	...	ad	6 oz. (170 ml.).

Infective Seborrhoeic Dermatitis and Sycosis

In this state pyogenic organisms give rise to a chronic pustular folliculitis of beard area and sometimes of scalp and pubes, blepharitis, and a low-grade, fissured dermatitis of flexures behind ears, angles of mouth, scalp, axillae, pubes, genitals and perineum, and other parts. This may light up into a more active, exudative eruption, with foul-smelling pus and scabbing. The organisms concerned are mostly staphylococci and non-haemolytic streptococci.

As local measures the halogen products of β-oxyquinoline are most valuable, particularly "steroxin," but also "quinolor" and "vioform." They are best used as ointments but may be incorporated in other pastes such as zinc paste, or tar paste if there is much irritable eczematization. Sensitiveness and irritation from these are uncommon. Other effective local treatment includes antibiotics, preferably those not used for internal therapy, such as neomycin, bacitracin, gramicidin, and others. They can be incorporated in a variety of ointments. Though in principle it is not a sound procedure, sometimes the combination of such antibiotic with hydrocortisone is valuable when applied for short periods in cases of localized infected dermatitis behind the ear or in the perineum. The aniline dyes, such as gentian violet 1%—generally used in an ointment or paste—are also beneficial, but stain clothes and skin badly. Brilliant green ½% combined with perchloride of mercury ½% in spirit as a lotion is also valuable for sycosis and infected seborrhoeic dermatitis, as is the careful use of Dalibour water, in full strength or diluted with equal parts of water:

Zinc sulph.	...	...	6 gr. (0.4 g.).
Cupri sulph.	...	...	4 gr. (0.26 g.).
Aq. camph.	...	ad	1 oz. (28 ml.).

Potassium permanganate baths (1 in 8,000) may usefully precede some of these measures if the condition is widespread.

It is generally desirable to supplement such local treatment with chemotherapy internally as sulphatriad 0.5 g. three times a day or sulphamethoxypyridazine ("lederkyn") 1 tablet daily for a few weeks, or an antibiotic as mentioned above. There is no greater risk of sensitization eruption from such internal medication than there is from the use of these measures in general medicine. Steroid hormones internally are not usually helpful and may aggravate this type of eruption.

The occupation and the general medical and emotional health of the patient suffering from infective seborrhoeic dermatitis and sycosis are matters for serious consideration; working in hot dusty atmospheres may seriously aggravate the condition, as may a state of physical debility, especially if associated with a focus of chronic infection, perhaps in the upper respiratory tract. Mental depression, which may readily follow such a skin disease, may also affect it adversely, especially in the serious-minded, over-conscientious, perfectionist type of patient.

Rosacea

Rosacea is an interesting affection in that it is limited to the face, is largely dependent on vasomotor instability and consequent variable flushing, and is particularly seen in women at the menopause. The associated eruption of granulomatous papules, often tuberculoid, in the skin which come and go in the course of days but may undergo degeneration, necrosis, and secondary infection, is also a unique feature of the disease. Similar lesions may affect the conjunctiva and over the cornea may produce serious ulceration. Usually both hormonal imbalance and emotional instability afflict these subjects, but on occasion toxic influences, even tuberculosis, may play a part. Other symptoms such as dyspepsia, palpitations, sweating, circulatory instability, and nervousness—symptoms closely resembling those of hyperthyroidism — are associated and aggravating but not causative features.

The response to local treatment is usually dramatic and is almost a diagnostic test. The patient should avoid soap and water, use a 2% sulphur and salicylic acid ointment at night, and receive very small unfiltered doses of *x* rays (50 r) once, twice, or thrice at 21-day intervals. Other ointments such as mercurials or even the ointment bases may be as effective as sulphur and salicylic acid, but not as consistently. Cosmetics used by day are of value as bland and protective applications, for exposure and heat aggravate rosacea.

Involvement of the cornea (5–10% of patients) was in the past often serious but to-day is usually controlled readily by 1% hydrocortisone locally.

Internally it is generally desirable to give a small dose of sedative (phenobarbitone ¼ gr. (16 mg.) or sodium amytal 1 gr. (65 mg.) twice a day or a tranquillizer such as chlorpromazine ("largactil") 10 mg. three times a day. Menopausal symptoms may require treatment independently.

Hydrochloric acid by mouth, as in the following mixture, taken once a day in a glass of water as a beverage with the main meal may be useful, probably by relieving flatulent dyspepsia which is often present:

Acid. hydrochlor. dil. ...			30 minims (1.7 ml.).
Glycer. pepsin. ...	...		1 dr. (3.5 ml.).
Syr. aur. ...	...	...	30 minims (1.7 ml.).
Aq.	...	ad	½ oz. (14 ml.).

A little dietetic care is wise, especially the avoidance of gastric irritants and stimulants and particularly hot, strong tea.

For no very clear reason antibiotics (penicillin, chlortetracycline) or sulphonamides given internally may produce rapid improvement, probably by controlling the common secondary infection, but possibly because the original papular eruption is in part dependent upon the activity of skin organisms.

Apart from the general sensitiveness and lack of confidence, patients with rosacea are not uncommonly reacting to stress, the understanding and relief of which may be essential to recovery.

The disease is apt to recur, usually at long intervals over the course of years, but this depends on circumstances. Attention to general health naturally

reduces the tendency. Rosacea arising in patients other than women at the menopause is usually responsive to similar treatment.

Body Odour

Distress to the patient and offence to society may arise from body odour. This is very variable racially and individually and is influenced by sex, age, emotion, and by health and tone generally, as well as by diet. In the main it is dependent upon apocrine secretion and so upon sex hormones. It is the decomposition of apocrine sweat by surface organisms that is responsible for odour, so that cleanliness and care of underlinen is very important. In addition, shaving the axillae and the use of an antiseptic deodorant locally may be indicated. Hexachlorophane detergent 0.5% is of value, as is a 25% solution of aluminium chloride or a saturated solution of bicarbonate of soda (Shelley, 1953). It is doubtful if chlorophyll is a direct deodorant.

The administration of oestrogens by mouth as suggested for acne, but in larger dosage, such as stilboestrol 1 mg. daily, appears sometimes to reduce apocrine activity.

REFERENCES

Beare, J. M., Cheeseman, E. A., Gailey, A. A. H., and Neill, D. W. (1958). *Brit. J. Derm.*, **70**, 233.
Ingram, J. T. (1957). *Arch. Derm. Syph. (Chicago)*, **76**, 157.
Rothman, S. (1954). *Physiology and Biochemistry of the Skin*. Chicago University Press.
Shelley, W. B., Hurley, H. J., and Nichols, A. C. (1953). *Arch. Derm. Syph. (Chicago)*, **68**, 430.

NIGHT CALLS: THEIR FREQUENCY AND NATURE IN ONE GENERAL PRACTICE

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The night call may be described as the bugbear of general practitioners, but relatively little is known about how often night calls occur, or about their nature. Various studies of general practice have reported the number of such calls in different practices, and these estimates vary greatly.

The aims of the present study were to ascertain not only how often night calls occurred in this practice and how their frequency varied at different times of the year and days of the week, but also the reasons for patients making such calls, the doctor's diagnosis, and the action which he took.

Details of 254 consecutive night calls were recorded in a ledger in which there were columns for the date, time, period the doctor was at the call, the patient's name, address, age, and sex, the reason given by the person putting in the call for wanting the doctor, the doctor's diagnosis, and his immediate and subsequent treatment.

The Practice

This practice is classified as semi-rural, and is situated in Penicuik, some 10 miles south of Edinburgh. There are four doctors, all principals, in the practice, and the number of patients registered with them was 9,023. Penicuik burgh had a population of 5,789 at June 30, 1956, and it is probable that the great majority of the Penicuik population were patients of this practice, as no other doctors have surgery premises there. The practice extends approximately 7 to 10 miles in each direction from Penicuik. Paper-making is the main industry in Penicuik, and the surrounding area is largely a farming community.

Frequency of Night Calls in Other Studies

Previous studies of general practice in which the number of night calls have been recorded have all been in urban areas. Brotherston and Chave (1956), studying a new housing estate, reported 70 consultations between 8 p.m. and 8 a.m. in a period of one year and related to 3,710 patients. Fry (1952) in his practice in the urban outskirts of London reported 110 visits between 8 p.m. and 7 a.m. in a year's study of his 4,456 patients. In the urban practice of 3,084 patients studied by Backett, Heady, and Evans (1954) there were 120 calls between 8 p.m. and 8 a.m. in a year. These represent annual rates of 19, 25, and 39 per 1,000 patients—a considerable variation.

Another series of figures, so far unpublished, is provided by D. McVie (personal communication), of Edinburgh. In his practice in the centre of Edinburgh he recorded an average annual rate of 84 calls between 8 p.m. and 8 a.m. per 1,000 patients, over a period of four years. This last rate is more than twice as great as that of Backett *et al.*, and more than four times that found by Brotherston and Chave.

Maternity work will account for some part of this variation but can hardly explain all of it. Over two-thirds of the calls recorded by McVie were between 8 p.m. and midnight, and the rate of calls between midnight and 8 a.m. was 25 per 1,000 patients per year. Unfortunately, comparable data are not available for the other three practices.

None of these earlier inquiries give any information about the type of call involved.

Frequency of Night Calls in this Study

In this inquiry "night" was taken to be the period from 11 p.m. to 8 a.m. The 254 calls studied occurred between November 8, 1955, and June 8, 1957, a period of 19 months. The number occurring during the calendar year 1956 was 155. This, in a practice of 9,023 gives an annual rate of 17 per 1,000 patients, but since "night" in this study is much shorter than that in the studies of Brotherston and Chave, of Fry, and of Backett *et al.*, it is not possible to compare this rate with their data. A comparison with McVie is, however, possible if calls between 11 p.m. and midnight are excluded, as he divides his calls into those before and those after midnight. The former constituted 30% of the calls in the present series, so that the annual rate for calls between midnight and 8 a.m. per 1,000 patients were 12 in this practice and 25 in that of McVie. We

have already seen, however, that his rate for 8 p.m. to 8 a.m. was between two and four times the rate in the other studies.

From the very limited amount of evidence that exists it would seem that the number of night calls in this practice is not atypical of other practices—although this is based on comparisons with urban areas only.

The proportion of nights on which there were different numbers of night calls was:

No. of Calls in a Night	Proportion of All Nights
0	65%
1	27%
2	6%
3 or more	2%

In this practice of 9,023 patients there were no calls between 11 p.m. and 8 a.m. on two thirds of the nights.

It is sometimes argued that night calls do not occur at random, but for various reasons, such as epidemics, seasons of the year, days of the week, they are clustered in such a way that there are an unexpectedly high proportion of nights with several night calls. The figures in this study do not support this argument, since the distribution of night calls is similar to a theoretical distribution calculated on the assumption that calls occur at random.* This enables us to calculate the probable number of nights with a call in a year in practices of different sizes and with different rates of night calls.

TABLE I.—*Expected Annual Number of Nights with One or More Calls Between 11 p.m. and 8 a.m. in practices of Different Sizes, with Different Rates of Night Call*

Size of Practice	Annual Rate of Night Calls per 1,000 Patients*		
	9	18	36
2,000	17 (5%)	34 (9%)	66 (18%)
4,000	34 (9%)	66 (18%)	119 (33%)
8,000	66 (18%)	119 (33%)	201 (55%)
16,000	119 (33%)	201 (55%)	291 (80%)

* These three correspond roughly to the rate of the present practice (18), half that rate (9), which may be similar to that found by Brotherston and Chave, and twice that rate (36), which is likely to be that found by McVie if calls between 11 p.m. and midnight were included.

A doctor in a practice of 2,000 and a relatively low rate of call may expect to be called out on only one night in 20, while a doctor doing night duty for a large practice of 16,000 may expect to be called out one night in three, in a practice with a low rate of call, and four nights out of five if the practice has a high rate. Moreover, in this last case he will expect to be called out only once on a third of the nights, twice on a quarter, and three or more times on a fifth.

Time, Day, and Season of Calls

The times the various calls were received are shown in Table II. Nearly a third of them occurred before midnight, and nearly half in the first two hours of the period. After 1 a.m. the distribution was fairly even. This early peak may be the result of patients feeling the need for a doctor's reassurance, before they settle down for the night.

TABLE II.—*Times of the 254 Calls*

11 p.m.–before midnight	30%
12 midnight–before 1 a.m.	15%
1 a.m.–before 2 ,,	9%
2 a.m.–	11%
3 a.m.–	7%
4 a.m.–	5%
5 a.m.–	9%
6 a.m.–	6%
7 a.m.–before 8 a.m.	8%

*This theoretical distribution is known as the Poisson, and is calculated by the formula $\frac{m^r e^{-m}}{r!}$, which gives the relative expected frequency of nights with r calls when m is the average frequency of night calls (e is the base of natural logarithms).

Night calls were fairly evenly spread on the different days of the week (Table III). There were slightly fewer than average on Sunday and more on Friday, but the difference might have occurred by chance in such a small series.

TABLE III.—*Day of Week of 254 Calls*

Sunday	11%	Thursday	15%
Monday	14%	Friday	17%
Tuesday	16%	Saturday	14%
Wednesday	12%	Unknown	1%

If we consider the four seasons of the year we find most consultations in winter, followed by autumn, spring, and summer:

	No. of Consultations
Winter: December–February*	47
Spring: March–May*	34
Summer: June–August	31
Autumn: September–November	40

* Averages based on two years' experience.

Age and Sex of Patients Making Night Calls

Unfortunately no age-and-sex analysis of the entire practice was available, but if it is assumed that the age-and-sex structure was similar to that of the population of Penicuik in 1951, certain comparisons can be made.

Of the night calls 135 were to female patients, 117 to males, and in two cases the sex of the patient was not recorded. If maternity cases are excluded as well as calls to patients for whom the sex was not recorded, 48% of the remaining night calls were to females. This may be compared with the proportion of women in the population, which was 53%. However, this difference might well arise by chance in a series of this kind, and we cannot conclude from these figures that males make relatively rather more night calls than females. There were, however, considerable differences for people in different age groups (Table IV).

TABLE IV.—*Age Groups of Patients Making Night Calls Compared with Estimates for Practice Population*

Age in Years	Patients Making Night Calls*	Estimate of Practice Population
Under 5	11%	10%
5–14	8%	15%
15–44	38%	43%
45–64	24%	22%
65 and over	19%	10%

* There were 23 calls for which the patient's age was not recorded, but reasons for call suggest that these people were not confined to any one age group.

Among those responsible for night calls there was a relative excess of older patients, aged 65 or more, and few schoolchildren.

Reasons Given for Asking Doctor to Call

The reasons given at the time either over the 'phone or by word of mouth for asking the doctor to call varied a great deal both in the amount of information they conveyed and in the form in which it was given.* On occasion the patient or person calling had already made the diagnosis—asthma, miscarriage—although the majority of people gave a description of symptoms which usually involved pain, such as sore ear, gasping for breath, or pain in stomach; while in a few cases the doctor was given very little indication at all of what was involved—a 'phone call by a neighbour to say a baby was very ill, or a request by a mill for a doctor's services.

*Normally the doctor received the 'phone call, but sometimes it was a caretaker.

Five groups of symptoms or conditions have been distinguished and two-thirds fell into these groups, but the remaining third cover a very wide range of statements.

TABLE V.—*Reason Given by Person Making Call for Wanting the Doctor*

Maternity	9%
Respiratory symptoms, pain in chest	18%
Abdominal ,,	24%
Haemorrhage	6%
Accidents, injuries	10%
Other	33%

In a quarter of the cases abdominal symptoms such as stomach-ache, vomiting, or diarrhoea were reported. The next most frequent group, accounting for nearly a fifth of the calls, were respiratory symptoms and pains in the chest, and asthma and difficulty in breathing were the main conditions included in this group. Accidents and maternity cases each were reported in about a tenth of the cases, and different types of haemorrhage—nose bleeds, coughing up blood, etc.—in 6%. Included in the miscellaneous group are such different things as "shaking all over," "in agony with bladder trouble," "think he's dead," "taken overdose of sleeping tablets," "think she has had heart attack," and "the baby is delirious."

However, these statements do not provide any reliable indication of the extent of the doctor's knowledge about each case when he sets out to visit it. To be told on the 'phone that Mrs. Burns has had another turn may indicate to him precisely what is involved, but it cannot be classified with any precision. On the other hand, the symptoms described on the 'phone may be a better indication of the anxieties that cause people to call the doctor out at night than the formal diagnosis that the doctor makes when he has seen the patient.

The Doctor's Diagnosis

The diagnoses recorded by the doctor have been classified according to the W.H.O. *International Statistical Classification of Diseases, Injuries, and Causes of Death.* The broad groups are shown in Table VI. The largest group is that of diseases and

TABLE VI.—*Doctor's Diagnosis*

Broad Group	%
Infective and parasitic disease	3
Neoplasms	1
Mental, psychoneurotic, and personality disorders	5
Diseases and symptoms of the nervous system and sense organs	10
,, ,, ,, ,, ,, circulatory system	12
,, ,, ,, ,, ,, respiratory system	12
Asthma	4
Diseases and symptoms of the buccal cavity, stomach, and duodenum	8
Diseases and symptoms of the abdomen and lower gastro-intestinal system	13
Diseases and symptoms of the genito-urinary system	4
Deliveries, and complications of pregnancy, childbirth, and the puerperium	11
Accidents	12
Others	5

symptoms of the abdomen and lower gastro-intestinal system. The most frequent diagnoses in this group were appendicitis and cholecystitis, but in a number of cases the doctor only reached a symptomatic diagnosis. This group accounted for 13% of the calls. Diseases and symptoms of the respiratory system accounted for 12%, and here the most frequent diagnoses were bronchitis and acute upper respiratory infection. Arteriosclerotic and degenerative heart disease was the most common diagnosis in the group of diseases and symptoms of the circulatory system which accounted for 12% of the calls. Accidents and maternity cases accounted for 12% and 11% respectively. Included in the group of diseases and symptoms of the nervous and sense organs were a number of vascular lesions affecting the central nervous system, and three cases of epilepsy. Ulcers of the stomach and duodenum and gastritis accounted for the majority of diseases and symptoms of the buccal cavity, stomach, and duodenum.

How far did the reason given for asking the doctor to call provide any indication of the diagnosis? This is examined in Table VII. Maternity cases and

TABLE VII.—*Reasons Given for Asking Doctor to Call Compared with Doctor's Diagnosis*

Broad Group	Reason Given for Asking Doctor to Call						Total
	Maternity	Respiratory System, etc.	Abdominal Pain	Haemorrhage	Accidents	Others	
Infective and parasitic diseases	—	—	5	1	—	2	8
Neoplasms	—	1	—	—	—	2	3
Mental, psychoneurotic, and personality disorders	—	2	1	—	—	10	13
Diseases and symptoms of the nervous system and sense organs	—	2	—	1	1	20	24
Diseases and symptoms of the circulatory system	—	14	2	1	—	14	31
Diseases and symptoms of the respiratory system	—	11	3	6	—	9	29
Asthma	—	10	—	—	—	1	11
Diseases and symptoms of the buccal cavity, stomach, and duodenum	—	2	13	2	—	3	20
Diseases and symptoms of the abdomen and lower gastro-intestinal system	—	—	30	—	—	3	33
Diseases and symptoms of the genito-urinary system	—	2	7	—	—	2	11
Deliveries and complications of pregnancy, childbirth, and the puerperium	22	—	—	5	—	1	28
Accidents	—	1	1	—	23	5	30
Others	—	—	1	—	1	11	13
Total	22	45	63	16	25	83	254

accidents were the only descriptions which nearly always tallied with the doctor's diagnosis. Chest complaints and abdominal symptoms each arose in a wide variety of diagnoses.

We have already shown that 30% of these night calls occurred in the first hour, between 11 p.m. and midnight. A relatively high proportion of calls which were diagnosed as being for either accidents or disease or symptoms of the stomach, duodenum, or buccal cavity occurred before midnight. Maternity cases were more evenly spread throughout the period: one in five was between 11 p.m. and midnight, while 12 of the 28 occurred in the two hours between 2 a.m. and 4 a.m.

An analysis by length of time of the call* shows, not unexpectedly, that maternity cases tended to take rather longer than other types of call. Over half the maternity cases took an hour or more, and one in five took two or more hours. This compares with 10% and less than 1% of the other calls.

Length of Call		Length of Call	
Less than 15 minutes	4%	45–1 hour	11%
15–30 minutes	22%	1 hour–2 hours	13%
30–45 minutes	48%	2 hours or more	2%

Individuals With More Than One Call

It should be stressed here that the term "cases" has been loosely used throughout this paper simply to denote night calls, and does not refer to individuals or illnesses. In fact, 215 individuals were involved in the

*Travelling time was included in this.

254 calls. Of the 24 people with more than one call seven had two calls on a single night. The actual distribution of night calls by individuals was:

No. of Night Calls	No. of Individuals
0	8,808
1	191
2	17
3	4
4	1
5	—
6	1
7	1

Of the 9,023 patients, 24 (0.27%) were responsible for a quarter of the night calls.

It seems, therefore, worth looking at the individuals who made more than one night call and their illnesses. The individual with seven calls was a woman aged 53 with a gastric ulcer and an anxiety state, and it was acute abdominal pain which caused her to call the doctor each time, although the doctors recorded a diagnosis of anxiety state on one occasion, gastric ulcer on three occasions, and abdominal pain or pyloric spasm on three. The individual with six calls was a man of 55 with asthma, and on each occasion he had an asthmatic attack and was given an injection. The man with four calls was an epileptic, but two of his calls were for abdominal symptoms. Of the remaining persons with two or three night calls 10 were males and 11 females, and their ages, from under 1 to over 80, were as varied as their conditions.

Are Most Night Calls Necessary?

Whether a doctor is called out in the night to a patient with a particular condition will depend on many things, such as the person's tolerance of pain or discomfort, his expectation of what the doctor can do for him, and his previous experience of the condition; it is also likely to be related to his relationship with and experience of his doctor. A general practitioner who is asked whether a particular call was necessary or not will take many things into consideration; not only the danger to the patient's life and health and the need to exclude certain diagnoses, but the patient's or his relatives' need for reassurance, and also possibly whether he, the doctor, was actually asleep at the time, the distance of the journey, and the weather. Any assessment, then, is bound to be highly subjective.

Of these calls 92% were regarded by the general practitioners involved as being necessary; 6% (15) were recorded as unnecessary, and 2% were not classified.

The number of calls regarded as unnecessary is too small to make a detailed analysis useful, but all types of diagnoses were involved, similar proportions of males and females, and people of all ages. Of the 63 calls from people making more than one call in the period, three were recorded as unnecessary—a similar proportion to all the calls.

Summary and Conclusions

The 254 consecutive calls arising between 11 p.m. and 8 a.m. in a semi-rural practice of 9,000 patients are analysed. The number of such calls arising in a year per 1,000 patients falls approximately in the centre of the range of rates found in other studies. It is estimated that a doctor with a practice of 2,000 and a similar rate of night call would expect to be called out on 34 nights in a year, and his chance of being called out on any one night would be slightly less than one in ten.

Nearly a third of the calls occurred between 11 p.m. and midnight. There was little or no variation in the numbers occurring on different days of the week, but, not unexpectedly, more calls arose in the winter months and fewer in the summer.

A relatively high proportion of the calls were to elderly patients and few to schoolchildren.

Abdominal symptoms, chest complaints or respiratory symptoms, and maternity cases were the reasons given by the person putting in the calls for asking the doctor to call in half of the cases.

Only 20 calls were not regarded by the doctor concerned as being necessary. This suggests an annual rate of about two " unnecessary " night calls per 1,000 patients.

There was no evidence to suggest that either patients making " unnecessary " calls or those who made more than one call during the period tended to come from any particular age or sex group, nor were these calls confined to any one type of condition.

These results were analysed by a group of D.P.H. students, Drs. Bolt, Buchanan, Chaudhuri, Hutchinson, McLean, Penman, Robertson, Ross, Saave, Scott, Sharp, Simpson, Wallace, and Weyndling, whose assistance is gratefully acknowledged.

REFERENCES

Backett, E. M., Heady, J. A., and Evans, J. C. G. (1954). *Brit. med. J.*, **1**, 109.

Brotherston, J. H. F., and Chave, S. P. W. (1956). *Brit. J. prev. soc. Med.*, **10**, 200.

Fry, J. (1952). *Brit. med. J.*, **2**, 249.

COLLEGE OF GENERAL PRACTITIONERS

SYMPOSIUM ON THE USE OF DRUGS IN GENERAL PRACTICE

Lack of knowledge of what is saved, in economic terms, by the use of drugs was deplored by the opening speakers at the College of General Practitioners' symposium on " The Use of Drugs in General Practice " on November 22. The symposium was sponsored by the Wellcome Foundation Ltd., and was held at the Wellcome Building, London. Two of the speakers were members of the Hinchliffe Committee, the third a member of the Scottish equivalent, the Douglas Committee. It was announced during the symposium that representatives of the College of General Practitioners had met representatives of the pharmaceutical industry about trials of drugs under general-practitioner as well as hospital conditions.

Hinchliffe Report

Professor C. A. KEELE, professor of pharmacology at the Middlesex Hospital Medical School, said that the drug bill was rising, as was the cost of other aspects of the Health Service as a whole. The increase in cost was related largely to proprietaries, the proportion of which to total prescribing was not, however, as high in Britain as in France (75%), Germany (85%), or Italy (90%). The Hinchliffe Committee had asked the Ministry of Health for an estimate of the savings in financial terms as a result of drugs, but information on this had not been forthcoming. Nor had this been the only occasion on which the Committee had been unable to get information from the Ministry.

About one-third of the sales of the pharmaceutical industry in this country was to the National Health Service, and one-third went in export. In the British pharmaceutical industry £4m. a year was spent on research, compared with £40m. in the United States and £7m. in Switzerland. The

industry in Britain spent more on research than was available to the Medical Research Council for all its activities: one firm might spend £1m. Pharmaceutical research involved long-term planning, and there were big risks commercially. The cost of research, which was borne by the profits from proprietaries, had to be taken into account if this country was to continue to receive the benefits of new discoveries. This might be done by encouraging those firms which did genuine research as compared with those who did not.

The Hinchliffe Committee had recommended that there should be a new publication, controlled by the medical profession through the Colleges and the B.M.A., to give independent information on drugs, and also that an organization should be established to enable firms to get in touch with people capable of doing clinical research.

Dr. H. C. FAULKNER, a general-practitioner member of the Hinchliffe Committee, said some people would have liked it to have found evidence of extravagance and irresponsibility in prescribing. It was pleasant for the general practitioners on the Committee to find that not only were their problems understood by their colleagues and all officers of the Ministry who gave evidence, but that there was no evidence of extravagance. Of the lack of information, Dr. Faulkner said that far from finding a vast bureaucracy they had found a very small staff in the Ministry, grossly overworked and with the minimum of the statistical information which any large industry would regard as essential.

The Hinchliffe Committee, Dr. Faulkner stressed, had endorsed the independence of the doctor to decide on the use of drugs. There was little evidence of pressure from patients—Dr. Faulkner did not believe that lists could be built up this way even in housing estates. America had a duplicated information sheet on drugs which was very hard-hitting indeed and which really went for manufacturers when this was thought necessary. The Committee felt that general practitioners wanted to be given all the facts and then left to form their own judgment.

Clinical Trials

Dr. E. VON KUENSSBERG, general-practitioner member of the Douglas Committee, said that in Scotland if preparations from the *British National Formulary* were prescribed instead of proprietaries it would be possible to save 4% of the drug bill—a small figure, but enough to build a new hospital and run it.

If a drug was submitted to clinical trial, it was reported on under hospital conditions and not general-practitioner conditions. This had, for example, resulted in much money being spent on tranquillizers until someone pointed out that amylobarbitone was just as good. The College of General Practitioners had now had a most successful informal meeting with the pharmaceutical industry on the question of testing drugs under general-practitioner as well as hospital conditions.

Discussion

Dr. J. D. W. WHITNEY (London) said it must be accepted that by prescribing more expensive drugs occasionally the greater expense of hospital admission was saved. Some proprietary preparations were better than preparations in the *British National Formulary*, and a few were cheaper. Undergraduates could well be taught by general practitioners: he could not see the consultant or registrar sitting down and teaching the pre-registration houseman about prescribing. Dr. K. M. FOSTER (Lincolnshire) said that, if the figures of rural dispensing practitioners approached those of town practitioners, they would be in the bankruptcy court.

Dr. J. A. D. ANDERSON (Edinburgh) said that figures in his practice showed that in what were commonly called stress diseases 60 prescriptions were dispensed per 100 consultations, whereas the major chronic illnesses had a prescribing rate of 40 per 100. The six doctors had an overall prescribing rate of 37 per 100 consultations, but one prescribed at a rate of 20 and another 45 per 100. According to J. P. Martin, frequency of dispensing was the most important factor in costs. Dr. A. J. WHITAKER (Guildford) suggested a relationship to the age of the practitioner, and Dr. J. C. G. EVANS (London) complained about the variety of names of drugs. Dr. H. E. THORN (Harrow) found the difficulty with young practitioners and students was that they did not know how much to prescribe. Some N.H.S. patients expected a large amount to be prescribed.

Dr. W. W. GERRARD (Banstead) asked where one could find what firms spent how much on research. Dr. H. SHIRE (Birmingham) said it was impossible for general practitioners to evaluate all the drugs coming on the market, and that therefore he reinforced the appeal for an independent publication. Dr. J. F. STEPHEN (Suffolk) had noted that he saw 34 different travellers more than 92 times during the year.

Dr. ALAN REZLER (London) considered the profession could well have a greater interest in the medical aspect of inadequate prescribing rather than a purely economic interest in high prescribing. Practitioners were perhaps too ready to accept themselves as having done something wrong. They might be doing a very fine job of prescribing, but at least one further set of figures was required—the cost per patient treated. A cost-per-patient-per-visit figure was too variable for comparisons between new practices, small practices, and large practices, since the last had a large body of patients who rarely presented themselves for treatment. Dr. I. GREGG (London) said that what to him was more important was the standard of prescribing. This was another aspect of the fundamental problem of the division between general practitioners and hospitals. He suggested pruning the medical course by a year and having a two-year pre-registration period, and that all doctors destined to be specialists should have at least six months in general practice. Dr. MARGARET DUDLEY-BROWN (York) said the amount of prescribing per prescription had increased since the shilling charge. She called for the exclusion of old-age pensioners from this charge. Hospitals could help more, with sensitivity tests.

Dr. H. D. P. LYTLE (Portsmouth) confessed to being a criminal. He had been arraigned before the local medical committee and exonerated. The Minister saw fit to turn down this decision and he then appeared before the appeal tribunal. Dr. Lytle read from the tribunal's decision: "Dr. Lytle gave evidence. He made two somewhat damaging admissions—that in prescribing he considers only the best kind of treatment to cure the patient quickly and that he does not think it wrong to prescribe the prescriptions recommended by consultants." Dr. P. HOPKINS (London) said the majority of patients did not require drugs but discussion of their problems. Until doctors had time to deal with them, they would continue to give drugs.

The opening speakers then replied.

ANNUAL MEETING

The seventh annual general meeting of the College of General Practitioners was held at B.M.A. House on November 21. Some 275 members and associates attended. Dr. F. M. ROSE, chairman of council, presenting the annual report, described the College's progress. More than 5,500 members and associates had joined the College since its foundation; 344 candidates recommended by the Board of Censors this year were admitted to membership, and 345 to associateship. The number of faculties in the United Kingdom and Eire remained at 25, in New Zealand four, and in Kenya one; four new overseas faculties had been formed in South Africa—the Witwatersrand, Cape of Good Hope, East Cape, and Natal Coastal Area faculties—making 34 regional faculties in all.

Education and Research

In the field of undergraduate education the College was proud of its student-attachment scheme, its undergraduate

teaching register (with 1,300 names), of the lectures to medical students and medical societies given by members of the College, and of its rapidly improving liaison with the staffs and students of medical schools. In postgraduate education, faculties had been particularly active, helped by the generous Pfizer grants. Two most successful College conferences had been held in London on "Dyspepsia" and on "Public Health and the Family Doctor," and in Manchester the North-west England faculty had organized a symposium on "Coronary Artery Disease" which had been attended by more than 500 general practitioners. The College's Medical Recording Service was proving to be an outstanding success. The journal of the College, published quarterly, was becoming increasingly valuable; and the memorandum for the guidance of trainers, published this year as one of its supplements, had been very well received. The amount of work done by the College's research organization continued to surprise everyone. With nearly 700 names on the *Research Register*, seven College-sponsored projects had been completed and published; 16 more were under way. Forty-two faculty-sponsored projects had been undertaken, of which the results of 18 had already been published. A large number of doctors had visited the Practice Equipment and Premises Room at College headquarters. The library was rapidly growing in size and scope; its photocopying service, financed by Messrs. John Wyeth and Brother Ltd., would soon start work to enable members or associates to obtain, free of charge, copies of any medical articles they wanted.

Elections and Presentations

Dr. G. F. Abercrombie was unanimously elected *president* for 1959–60. Dr. I. D. Grant (Glasgow), Dr. L. H. Cordery (New Zealand), Dr. W. V. Johnston (Canada), Dr. H. M. Saxby (Australia), and two members of the steering committee—Dr. J. D. Simpson (Cambridge) and Dr. J. Campbell Young (Belfast)—were appointed *honorary fellows* of the College.

Dr. T. E. T. Weston (London) was presented with the *Butterworth Gold Medal* (1958–9) for an essay on "The Child is Father of the Man." The subject for the 1959–60 Butterworth gold medal will be "Television and Health"; essays must be submitted to the chairman of the awards committee not later than September 17, 1960. 16 *Upjohn Travelling Fellowships* (up to £200 each) were presented to: J. A. D. Anderson, J. B. Bamford, S. J. Carne, P. F. Cawley, M. B. Clyne, S. D. Coleman, G. R. Cubitt, Katharina Dalton, Margaret Dudley-Brown, F. B. P. Evans, J. S. Happel, P. D. O'Beirne, D. C. Saunders, M. T. Sweetnam, F. F. Temple, and G. H. Warrick. 6 *Public Welfare Foundation prizes* (£40 each) were presented to the following final-year students: J. G. Adamson, M. L. Dorfman, Bridget Hackett, and D. A. Shedden (all of Edinburgh University), A. Barabas (Manchester University), and W. S. Marson (Glasgow University). The following *faculty representatives* were appointed to the Seventh College Council (1959–60): O. Plowright (North London), G. S. R. Little (South London), E. A. W. Marien (East London), R. Cove-Smith (West London), George Swift (South-east England), J. C. T. Sanctuary (Northern Home Counties), W. G. Tait (Thames Valley), J. C. Leedham-Green (East Anglia), R. M. S. McConaghey (South-west England), D. L. Crombie (Midland Faculty), K. M. Foster (North Midlands), R. A. Murray Scott (Yorkshire), S. Freeman (North-west England), G. L. Hindson (North-east England), W. L. Selkirk (Merseyside and North Wales), J. N. M. Parry (Welsh Faculty), Richard Scott (South-east Scotland), W. S. Gardner (West of Scotland), J. M. Henderson (East Scotland), G. Swapp (North-east Scotland), G. H. Clement (North Scotland), A. S. Boyd (Northern Ireland), V. G. Doyle (East of Ireland), J. P. J. Little (West Ireland), J. I. O'Sullivan (South Ireland), L. R. Hetherington (Auckland), H. E. W. Roberton (Canterbury), H. E. M. Williams (Otago), A. A. Tennent (Wellington), Mary Robertson-Glasgow (Kenya), G. W. Schepers (Witwatersrand), and F. E. Hofmeyr (Cape of Good Hope). Four *elected members of council* to replace those retiring were appointed: H. L. Glyn Hughes, R. Harkness, W. R. Hylton, and F. M. Rose.

College Business

A special resolution—"The time has now come for the College of General Practitioners to institute an examination for admission to membership; this to be introduced for those who will register with the General Medical Council (or equivalent organization) after January 1, 1960. The present criteria for membership will hold for those who have registered before that date"—received just less than three-fourths of the votes cast and was therefore lost. Ten recommendations from faculties were discussed, and three of the College's by-laws were amended.

The CHAIRMAN thanked the British Medical Association for its generosity in allowing the College the use of its Hall; and Dr. H. N. LEVITT moved a vote of thanks to Dr. Rose for all the excellent work he had done during his three years as Chairman of Council. At the meeting of the new council, held later, Dr. Annis Gillie was appointed chairman, Dr. K. M. Foster deputy chairman, Dr. H. L. Glyn Hughes hon. treasurer, and Dr. J. H. Hunt hon. secretary. Dr. I. D. Grant (immediate past-president) and Drs. J. F. Burdon, H. N. Levitt, and L. Lamont were appointed additional members of council.

SIXTH JAMES MACKENZIE LECTURE

INDUSTRIAL HEALTH AND THE G.P.

Reluctance by Government departments to accept responsibility for industrial medicine was such that one wondered whether this growing branch of medicine would not thrive better under a public corporation answerable to Parliament, Dr. J. A. L. VAUGHAN JONES told the College of General Practitioners when he delivered the sixth James Mackenzie lecture in the Great Hall, B.M.A. House, on November 21. He hoped that before long the special ethical rules for industrial medical officers would be "swept into an appropriate receptacle."

Much had been spoken and written in the last decade on health in industry, said Dr. Vaughan Jones: there had been too many words and too little action. His historical survey showed that interest in the subject dated back considerably further. As early as 1830 a Bradford employer had appointed a works doctor to watch over the health of the juvenile workers. Dr. Vaughan Jones paid tribute to the 1,800 appointed factory doctors. The huge areas covered by medical inspectors did not allow their potential to be fully realized, and the dead hand of the Treasury must be forced on this issue. In 1940 Mr. Ernest Bevin introduced the Factory and Welfare Order which made it incumbent on firms engaged in armaments manufacture to provide medical and nursing services. Unfortunately, too many of these appointments of works medical officers were of uniformed doctors who did no good to the cause of industrial health. In 1941 the B.M.A. published a report on industrial health in factories: progress in the intervening period had been slow.

Fitness to Work

Even in the relatively small but important matter of giving a certificate of fitness for work, had doctors accepted their proper responsibility? Did they know the work to be done, what it involved and its demand on the physical and mental systems of the patient, and its relationship to his total environment? Did they really know the total environment? Too often the answer was "No," and with the present standard of clinical teaching it was likely to remain so. In the ordinary curriculum very little was included on the relationship of industry, health, and diseases, and the emphasis, in Dr. Vaughan Jones's view quite wrongly, had been placed on postgraduate teaching. Unless there was a possibility that the subject would be included in the degree examination, the final-year student was tempted to discard or forget it.

"I just cannot understand why there has been so much reluctance by Government departments to accept the

responsibility for this growing branch of medicine, so much so that one wonders whether it would not thrive better under a public corporation answerable to Parliament," said Dr. Vaughan Jones. "There can be no excuse for a Ministry of Health with such limited horizons that it cannot see the close relationship of man at work with man at home—a Ministry with responsibility for an accident service, which believes in a concept of rehabilitation, yet cannot accept the close relationship of preventive and curative medicine as expressed in the association of an industrial scheme with hospital beds." In spite of this Dr. Vaughan Jones thought the Ministry of Health should be responsible. The Ministry of Labour, although closely associated with the Factory Department, was not the place for co-ordinating existing health services. The Ministry of Health should have overall supervision of all medical services in the country, but this would not prevent the Ministry of Labour having delegated responsibility for running an industrial health service. For small factories and places of work voluntary effort must first be given every chance, and, if this failed, then statutory health services must come in, and come in quickly.

Finally, referring to the "vexed question" of special ethical rules for industrial medical officers, Dr. Vaughan Jones was satisfied that what might have been useful some years ago when it was thought necessary to protect the interests of certain practitioners did not hold good to-day. Special ethical rules were no longer needed. The ordinary human and professional relationships between colleagues in all branches of the profession must be improved, but this did not apply only to industrial medical officers.

PROCAINE THERAPY IN OLD AGE

ADDRESS BY PROFESSOR ANNA ASLAN

[BY A SPECIAL CORRESPONDENT]

Professor ANNA ASLAN, of the C. I. Parhon Institute of Geriatrics, Bucharest, gave a lecture on "Procaine Therapy in Old Age and Other Trophic Disturbances" at the Apothecaries' Hall, London, on November 19. The occasion had been arranged and sponsored by the *Daily Mail* newspaper.

At a reception held immediately before the lecture, those present (mainly general practitioners) were given an opportunity to meet Professor Aslan, who speaks excellent French but, unfortunately, very little English. However, the numbers anxious to be introduced made it difficult for any one individual to talk to her at length, and certainly no detailed scientific conversation was possible. Nevertheless, she gave the impression that she was very willing to discuss her work.

The lecture itself began with a short appeal to the audience by a member of the staff of the sponsoring newspaper. He asked them to regard as confidential a summary of Professor Aslan's discourse which had been provided, and not to communicate it to other organs of the press. He also explained that the proceedings were being tape-recorded and that a transcript of the recording would subsequently be made available to any interested person who applied for one. Finally, he expressed regret that the announced chairman was unfortunately prevented at the last minute from taking the chair, and Dr. Elkin would preside in his place. Dr. Elkin then presented Professor Aslan, who began her address.

Regular Injections of Procaine

Reading in English from a prepared script, she started by expressing her pleasure in the occasion and paying tribute to the history of British achievement in the study of geriatrics. She spoke of her own indebtedness at the outset of her career to the written works of Sir James Mackenzie. At this point she began to speak in French and briefly outlined the background of study and research on which her present work was based. Professor Aslan then handed her manuscript to a translator who thereafter read it for her in English.

The translator said that the basis of Professor Aslan's treatment of the elderly was the regular intramuscular injection of courses of procaine in 2% buffered solution at acid *p*H of 4.3. The dosage was 5 ml. per injection, with three injections weekly to a total of 12. About 10 days' interval was allowed to elapse between each course of injections, and courses were continued more or less indefinitely. Before treatment each patient was tested for procaine sensitivity by intradermal or subcutaneous tests. Professor Aslan had called her solution H3.

The first series of cases so treated—in 1951—consisted of 25 elderly subjects with a variety of conditions including arteriosclerosis, senile Parkinsonism, pseudo-bulbar syndrome, and spondylosis. Professor Aslan showed a number of black-and-white and coloured lantern slides of these patients to demonstrate changes in their external appearance following treatment. But, as no two photographs of the same patient had been taken under the same conditions of lighting and background, these were not entirely satisfactory.

Professor Aslan claimed generally beneficial results for her patients, and cited elderly cases with depression and loss of memory who had subsequently sufficiently recovered their faculties under procaine treatment to be able to follow some form of useful occupation. She referred to the striking speeding up of reaction time in patients treated with H3, and showed a number of graphs. Unfortunately these were too lacking in detail to be understood easily, and in some the co-ordinates were not labelled. She also showed slides of radiographs claimed to indicate regression of joint lesions in cases of osteoarthritis.

Three groups of cases treated, respectively, with procaine, pineal-gland extract, and liposoluble extract of germinated wheat (containing vitamins E and F), and a fourth control group receiving symptomatic treatment only, were compared and contrasted. Only the group treated with procaine had shown improvement in the form of increase in weight and diminution of symptoms of degenerative change, it was said.

Professor Aslan then referred to certain investigations she had carried out on capillary permeability as affected by procaine. In subjects treated wth H3 she had observed a greater capillary permeability to fluids, to serum albumin, and to beta- and gamma-globulins. This, she felt, must in part be the cause of the beneficial effect of H3 on the course of some cases of arteriosclerosis.

Vitaminic Action

Then there was the "vitaminic action" of procaine which had led Professor Aslan to call her solution H3. She mentioned experiments on brewer's yeast and liver homogenate in which procaine had produced increased oxygen consumption, and other experiments on the metabolism of bacterial cultures. These, she thought, supported her view that procaine acted by way of its breakdown products, *para*-aminobenzoic acid and diethylaminoethanol. She then concluded her lecture with further general conjectures on the pharmacology of procaine, and by finally paying tribute to her co-workers and to others who had worked upon the subject.

After Professor Aslan had sat down, the audience were invited to submit written questions and a selection of these were put to her for immediate answer. However, none of these questions nor Professor Aslan's replies to them added greatly to what she had already said. The evening ended with a vote of thanks.

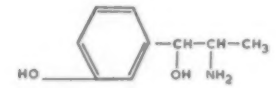
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Metaraminol bitartrate

"Aramine" (Merck Sharp and Dohme).

The chemical name of this substance is laevo-1-(*m*-hydroxyphenyl)-2-amino-1-propanol hydrogen d-tartrate. Its structural formula is as follows:



Pharmacology.—Metaraminol is a sympatheticomimetic amine with a systemic vasopressor effect. Its onset is more gradual and its action more prolonged than that of other pressor drugs, and thus smoother maintenance of blood pressure in hypotensive states may be achieved. It has the special advantage that it is not irritating to the tissues and may therefore be given subcutaneously or intramuscularly. If a leak into the tissues occurs during intravenous administration, no sloughing will result. In addition it appears to have little tendency to cause arrhythmias. Finally, animal experiments show that it has a myocardial-stimulating property as well as the pressor effect, though it is uncertain how great a role this plays in its therapeutic effect in man.

Clinical Effects.—Metaraminol is a useful pressor agent in combating hypotensive states during surgery and anaesthesia and in the treatment of shock. Most clinicians agree that, when cardiac infarction is accompanied by shock, some form of mild pressor therapy has a place in treatment, and metaraminol would appear to be one of the most favourable drugs for use, because of its smooth action and relative freedom from any tendency to produce arrhythmias and sloughing.

As a general method of administration 2–10 mg. may be injected subcutaneously or intramuscularly. When it is decided to use the intravenous route, 15–100 mg. diluted with 1 pint (0.6 litre) of normal saline or 5% dextrose may be given by slow drip, adjusted to maintain the blood pressure at the desired level. In emergencies, when severe shock is present, 0.5–5 mg. may be given directly into a vein.

Caution.—There are no definite contraindications to the use of metaraminol apart from the usual caution required when giving drugs that cause peripheral constriction to patients with systemic hypertension, heart or thyroid disease, or diabetes. When metaraminol is given intravenously undiluted, great care must be taken that the exact and correct dose is given. Since the effect of the drug is delayed up to five minutes after intravenous injection, up to 20 minutes after intramuscular, and up to 45 minutes after subcutaneous injection, a suitable time should be allowed to elapse before repeating the dose, so as to avoid the possibility of a cumulative effect.

N.H.S. Basic Price.—12 ampoules of 10 mg./ml. for injection, 20s.

A pamphlet called "The Middle-Aged Man," by Dr. ALFRED TORRIE, has recently been published for the Church of England Moral Welfare Council by the Church Information Office (price 1s. 6d.). It outlines the difficulties, physical and psychological, with which some middle-aged men find themselves faced, and gives advice to clergymen and others on how they can understand these difficulties and help the men concerned to overcome them.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

An Accident Service for the Nation

SIR,—The importance of our accident and casualty services is suitably stressed in your leading article (*Journal*, November 14, p. 1009) and in the report of the meeting of the British Orthopaedic Association (p. 1016), but before embarking on any quasi-military or other national operations to introduce new systems and new surgical empires we should pause to examine what really goes on at present in our casualty departments. It would be quite disastrous to abolish these departments as suggested at the orthopaedic meeting without providing alternative services for the many non-traumatic conditions that are seen by the young casualty officers.

The role of the casualty department in the hospital service must be reviewed, but until this role is carefully examined and analysed it would be impetuous to proceed along the revolutionary lines suggested. Much condemnation is heard of these departments, but there have been no worth-while definitive studies yet on what the casualty department does and how it is being done. There have been no analyses of the proportions of non-traumatic conditions dealt with. Certain preliminary observations show that in many departments the proportions are well over 50%. Who is to look after these patients who flock to the casualty departments? Why do these patients go there in the first place? Why do local general practitioners use these departments for a quick second opinion (by much junior colleagues), and also why do these same general practitioners have to try and get their urgent cases admitted through this department (causing an unfair burden on the young casualty officer)? Before any steps are taken to shut these departments and replace them by fewer and more specialized accident centres, the relations of the casualty departments with the local community and with local general practitioners must be carefully looked at. It is not only the casualty departments that are in trouble and at fault but also the public and the general practitioners who abuse them.

It is fortunate that the Nuffield Provincial Hospitals Trust has undertaken, and almost completed, a survey of casualty departments all over the country. This survey, which should add to our knowledge, has been carried out with the active help of the Ministry of Health, so it is rather unfair to insinuate a charge of "apparent indifference." Finally, surely it is wrong to blame delays on action and improvements on the "Ministry" and the "State." Is there not any scope here for local initiative? There is little to prevent each region, each area, and each hospital from looking at, and looking into, their own casualty services, defining their own local problems, and applying the simple and inexpensive remedies that are obvious as soon as such examinations are carried out.—I am, etc.,

Beckenham, Kent. JOHN FRY.

SIR,—How very welcome are Mr. H. J. Seddon's suggestions for an accident service for the nation (*Journal*, November 14, p. 1009). The post-war years have brought tremendous changes in our way of life. Full employment and the increasing number of women

employed; the spreading of industries and factories to the smaller towns and villages; the very great increase in the use of machinery both in the factory and at home; the tremendous increase in motor traffic. All these factors have resulted in an increased accident problem, spreading it more and more over the country as a whole. Whilst this has been going on little improvement has taken place in the facilities for the treatment of accidents, which are still too often handled in antiquated casualty departments often staffed by very junior members of the profession.

Experience in practice in the R.A.F. and 10 years of Ministry of National Insurance Industrial Injuries Medical Boards has left me with the unmistakable impression that we could do far more than is at present done for the injured person, who, all too frequently, is left with a disability for life. This is perhaps most noticeable among the less severe injuries to hand and foot.

How much easier it would be to run hospitals if the *x*-ray departments, their appointment systems, etc., were not subjected to the constant disorganization caused by accidents, road traffic accidents in particular.

It should be borne in mind that every accident carries with it the risk of disability, and therefore the prospect of such a service being able to improve the treatment of accident cases, lessen the time in hospital or off work, and reduce the number of permanent disabilities surely warrants the most careful study.—I am, etc.,

Berkhamsted. H. DENIS WHITE.

SIR,—I should like to congratulate you on your excellent leading article on the subject of an accident service for the nation (*Journal*, November 14, p. 1009). However, there is one sentence with which I disagree: ". . . an integrated peacetime national accident service would be of immense value to the nation in time of war."

It is widely held that a nuclear war would entail the complete destruction of this country. Therefore, unless our peacetime accident service operates from extremely deep underground shelters, the above statement is incorrect, and can only help to lull some of us into thinking a nuclear war would be "something like the last one, only worse," and so cause us to relax the pressure we must all put on our leaders, political and otherwise, to solve the disarmament problem.—I am, etc.,

London, S.W.11. J. FERGUS KING.

Leukaemia and Radiation

SIR,—In the leading article (*Journal*, October 3, p. 625) on our findings relative to maternal irradiation and subsequent leukaemia in the child[1] you inferred that the lack of a statistically significant difference in our groups (72 leukaemic; 58 control) was in opposition to the findings of Alice Stewart *et al.*[2] This, I feel, is a misleading interpretation. What should be emphasized is the fact that our report and others, such as that of Ford *et al.*,[3] are in agreement that the irradiated group develops a higher incidence of leukaemia. The only point of difference in the results of these studies is the magnitude of risk involved. Other investigations, such as were surveyed by Lewis,[4] would tend to indicate that the risk from such a small dosage of radiation is probably less than that found by Stewart *et al.* In any case a small series should not be expected to show an appreciable difference.

Our follow-up of 80% is, I feel, satisfactory considering that most families were lost to us for a period of years. Stewart *et al.*, you will recall, reports on only 83.6% despite a much smaller geographic scattering.—I am, etc.,

Glendale 3, California. DONALD W. POLHEMUS.

REFERENCES

1 Polhemus, D. W., and Koch, R., *Pediatrics*, 1959, **23**, 453.
2 Stewart, A., Webb, J., and Hewitt, D., *Brit. med. J.*, 1958, **1**, 1495.
3 Ford, D. D., Paterson, J. C. S., and Treuting, W. L., *J. nat. Cancer Inst.*, 1959, **22**, 1093.
4 Lewis, E. B., *Science*, 1957, **125**, 965.

Conspicuous Hearing-aids

SIR,—As a deaf person who uses a hearing-aid, I sympathize with the wish of Dr. D. H. Ropschitz (*Journal*, November 14, p. 1018) that a less cumbrous apparatus were available on the N.H.S. A general-issue aid, however, will have to be fairly robust, which the commercial transistor-aids are not. The manufacturer's guarantee of one for which I paid £60 lasts for only one year and does not cover damage caused by dropping the instrument.

But there is one aid to the deaf of all ages available in many areas, free, about which doctors and patients are often ignorant: instruction in lip-reading. Trained, experienced teachers exist in many hospitals who will teach the patient by himself or in small or large groups, as best suits his case. From my own experience I can vouch for the extraordinary gain which results from even a little accomplishment in lip-reading. The increased sense of communication is delightful. Almost every person who is not psychotic is capable, whatever his age, of getting some benefit from lip-reading, and a doctor in charge of the personal problems of a deaf person should do his best to have him taught to lip-read.

Finally, it is time and more than time that the general attitude to deafness and hearing-aids changed till they are taken for granted like short-sight and spectacles. Deafness is a disability, not a misdemeanour. Like all disabilities, it must be accepted and fitted into an integrated life. Like all disabilities, it is easier to accept if one knows it is common at all ages, that there are lots of other people like us. Doctors concerned with the psychological aspects of deafness cannot help us more than by adopting this candid and rational attitude.—I am, etc.,

Cambridge. A. M. PANTIN.

SIR,—The "Medresco" hearing-aid is condemned by Dr. D. H. Ropschitz (*Journal*, November 14, p. 1018) as archaic and conspicuous. There is some truth in his criticism, but there is a more important side to the picture. The N.H.S. aid is undoubtedly cumbersome by modern standards, but let us remember that it was designed over ten years ago when cost and ease of production were more important than appearance. It is a robust aid and its performance compares favourably with expensive commercial instruments; the original aid with separate batteries is being replaced gradually by an N.H.S. transistor model.

I think Dr. Ropschitz is wrong to stress the importance of concealing deafness. Conductive deafness is increasingly amenable to surgical correction, but patients with perceptive deafness must continue to rely on hearing-aids. Most of these cases are helped, but very few would pass as "normal." I therefore assure my patients that deafness is no longer considered a

stigma, and advise them to point out their handicap to their associates and they will usually receive consideration. This is much less damaging to the psyche than attempted concealment, which is bound to be unsuccessful. There is a lot of good sense in the old story of the salesman who sold a button on a string as a hearing-aid. When asked how it worked he replied, "Pop the button in your ear, and people will speak up when they see it."—I am, etc.,

Hull. J. S. MARTIN.

Recording Speech and Respiration

SIR,—The recent introduction of a non-electric tape recorder has made possible the recording of patient's speech under conditions which prohibited the use of non-portable recorders or of those which drew their power from the mains or high-voltage batteries. In recent years the recording of speech for clinical purposes has become commonplace; apart from its value as a complete verbatim record of an interview, it enables accurate analysis to be made of speech rhythm and other formal aspects of the articulatory process as well as of speech content itself.

The value of such a detailed analysis in the investigation of intracranial lesions has been shown by Monrad-Krohn[1]; Engler[2] has described its use in paediatrics, particularly in trials of drugs designed to improve the speech of spastics. In psychiatry it has an even wider application. Thirty years ago Golla and Antonovitch[3] described the relationship between respiratory rhythms and thought, and Goldman-Eisler[4] has described methods of measuring this relationship for the purpose of appraising the results of cathartic processes or psychiatric interviews.

Goldman-Eisler[5] has found a throat microphone to be sensitive enough to permit respiratory sounds to be measured during playback, but this appears to obtain only with an amplifier of high technical standard used under laboratory conditions. It has not proved suitable for use with the non-electric recorder, which has to be connected with a commercial radio amplifier; and even with the portable electric models normally used in hospitals and general practice the signal:noise ratio is too small for accurate monitoring of respiration sounds during concomitant speech recording.

The most effective method I have found makes use of a No. 4 B.O.C. facemask in which a throat microphone element has been inserted through the rubber. An airtight seal should be made by using a rubber filler solution, and the best position is lateral to the tube fitting. A two-way valve with independent operation is inserted into the facepiece opposite and symmetrical to the microphone.

Such a unit has a number of uses. It can be used to record speech during the early stages of anaesthesia—for example, it is being used currently during the administration of carbon dioxide for abreaction therapy. Connected to a CO_2-analyser,[6,7] it enables other aspects of respiratory physiology to be measured concomitant to speech verbalization and rhythm. As a portable accessory for speech-recording the tube fitting can be closed by a rubber bung, when it will be found that the juxtaposition of the valve to the microphone produces a shrill note during respiration that can be identified with ease even on a poor recording or using low-grade equipment. Further scope for its use comes from the recording or measuring of physiological variables during the administration of physical, neurological, or psychological tests.[8]

The use of such a respiratory restrictive device does, of course, alter the nature of breathing patterns to some extent. However, in those cases in which a mask is to be used anyway, this will not make any difference; in other cases, the effect is usually cancelled out in any form of inter-group comparison. It is interesting to note that with psychiatric patients the subjective reaction to the mild stressor effect actually produces finer diagnostic discrimination.—I am, etc.,

Summersdale Hospital, Chichester, Sussex. L. R. C. HAWARD.

REFERENCES

1. Monrad-Krohn, G. H., *Acta psychiat. scand.*, 1947, **22**, 255.
2. Engler, M., *J. ment. Sci.*, 1955, **101**, 391.
3. Golla, F. L., and Antonovitch, S., *Brain*, 1929, **52**, 491.
4. Goldman-Eisler, F., *J. ment. Sci.*, 1956, **102**, 78.
5. —— *Brit. J. med. Psychol.*, 1955, **46**, 53.
6. Haward, L. R. C., *Ind. J. Psychol.*, 1955, **30**, 111.
7. —— *Brit. med. J.*, 1958, **1**, 394.
8. —— *Rorsch. Newsletter*, 1957, **2**, 18.

Auscultation on the Gramophone

SIR,—I have to-day received an advertisement of a book running to 657 pages and costing £3 17s., which purports to assist the reader to auscultate the heart. "Normal heart sounds are described so graphically that you can almost hear them as you read . . . a definite encyclopaedia of all conceivable variations in sounds from the heart that you are likely to hear." Not having read the book, I am not in a position to say whether it achieves its purpose, but one can imagine the difficulty to both author and reader in conveying sound in words. I wonder how many hundred thousand words would be required to write a description of the tune of the National Anthem before it could be conveyed to someone who had never heard it.

What a wonderful opportunity there is for someone to produce a long-playing record of normal and abnormal heart sounds and rhythms with a descriptive commentary aimed at the average intelligence. Back numbers like myself whose education in auscultation ceased 25 years and more ago could refresh and re-orientate themselves in cardiology without moving from their firesides. The method seems attractive, easy, and effective. Could not the B.M.A. approach a wealthy drug-house for assistance in financing the project on the lines of I.T.V.—"These heart sounds are coming to you by courtesy of Smith's Iron Filings"? It would be too much to expect the Ministry of Health to sponsor a new approach to postgraduate education.—I am, etc.,

Sheffield, 8. E. C. ATKINSON.

Schultz–Dale Test for Carcinoma

SIR,—I have read with interest and concern the paper by Mr. L. M. McEwen (*Journal*, October 3, p. 615) covering his limited experience with the Schultz–Dale test for detection of cancer antigens which we described[1,2,3] and which was confirmed by Dr. Burrows.[4] Of course, any work in this specific area of the immunology of cancer appeals to me. However, Mr. McEwen's experimental procedures and the interpretation of his findings should be given a searching review. I believe they cannot go unchallenged.

It is generally realized that the Schultz–Dale test is not only one of the most sensitive immunological methods but is also one of the most intricate and difficult techniques to work with. It requires substantial experience before one may hope to obtain accurate results. The many variables that affect this biological equation make it susceptible to technical difficulties, and even the slightest deviation in technique can give rise to erratic results which, of course,

make any attempt at interpretation hazardous indeed. Because of limitation of space, I will refer to only two aspects: (1) Some of the "bugs" which have plagued Mr. McEwen's system of experimentation. (2) The serious misconception which he has made the centre of his theme.

Some of the apparent technical defects we note in his report are concerned with the preparation of Tyrode's solution. Mr. McEwen notes that he is using half-strength calcium (which we use) and which should be calcium chloride 0.05 g. per litre, but actually he is using full strength (i.e., 0.1 g./l.). This would undoubtedly explain the increased and abnormal irritability of the uterine muscle in his system. We have also found that magnesium ions are important in this system, and we use 0.1 g./l. —i.e., ten times the amount Mr. McEwen uses. The lack of an adequate supply of magnesium ions will tend to further increase uterine muscle irritability. Further precautions in the preparation of Tyrode's solution (and which I am not certain that Mr. McEwen is observing) should be exercised—viz., first, Tyrode's solution should be freshly prepared each day, and, second, its *p*H should be corrected to 7.4. Failure to follow these conditions will give rise to the undue irritability from which Mr. McEwen's system suffers and which he describes as "unpredictable sensitivity of the preparations to other stimuli and their frequent high level of spontaneous activity."

The grave misconception which Mr. McEwen's argument centres upon is the difference in behaviour between a sensitized uterine horn and a so-called "control" horn left unsensitized. But is this untreated horn a real control? If not, what type of controls should one adopt? The use of an unsensitized horn as a "control" carries a definite misconception and a false sense of security. Early in our work we have used this procedure in one experiment on sera from patients with other diseases than cancer to detect a pressor effect. We have since found that, when cancer tissue antigens or sera from cancer patients are added to the unsensitized horn, positive reactions appear in many of these.[5] To those who are newcomers to this type of work, this indicates nonspecificity—but does it?

Open sites on the surface of an unsensitized uterine horn are an invitation to the antibody molecules to become fixed there. This could happen in a matter of minutes. Once the antibodies are fixed these sera, which have an accompanying free antigen as well as antibody, would then give rise to a specific anaphylactic reaction in this so-called "control" unsensitized horn. That this could take place has been described earlier by Kulka.[6] More recently Trapani, Garvey, and Campbell[7] have clearly shown that soluble antigen antibody complexes can give rise to local anaphylactic response in the Schultz–Dale test when added to normal unsensitized guinea-pig smooth muscle. Evidently Mr. McEwen is not cognizant of this fact. He looked for differences between the sensitized horn and this false "control" unsensitized horn. When the differences he obtained between these two were not statistically significant he was ready to report that "carcinoma antigen was not demonstrated," while all the time, as a matter of fact, it has been there and actually exhibiting a dual show of its presence.

If we then exclude his findings with the "control" series which are not true controls and look into his sensitized series for some information, we find that in 19 out of 34 sensitized preparations (i.e., in 56% of cases) a positive reaction was demonstrable which is distinct from that obtained with normal tissue antigens (since this has been eliminated earlier by desensitization from the system). The fact that he obtained this definite evidence of desensitization to normal serum could only indicate one possibility—namely, that this was a specific immunological reaction to normal tissue antigens. Chase[8] emphasizes that, by demonstrating specific desensitization in a Schultz–Dale test, nonspecific causes of muscle irritation can be ruled out. Campbell[7] utilizes the same criterion. This desensitization to normal serum in Mr. McEwen's experiments will strongly suggest that the subsequent reactions which he obtained with cancer sera are in fact specific reactions also and indicate the presence of specific carcinoma antigens.

To provide the final proof for the specificity of these reactions with carcinoma sera, Mr. McEwen might well have resorted to what we did earlier[2] by attempting to obtain desensitization to these same positive sera, in which case he would have most probably found that these reactions are amenable to desensitization. They are therefore specific immunological reactions rather than pharmacological irritants. This method, in fact, of using the same horn as its own control and in which desensitization with positive serum is obtained is to me the best type control. For I know of no pharmacological muscle irritant which could give rise to this phenomenon. Thus we see that Mr. McEwen's case against the Schultz–Dale test is no longer tenable, and it seems clear that his difficulty lies primarily in technical procedure and his interpretation of findings rather than in the Schultz–Dale test itself.

In approaching this new field of cancer immunology, let us discard some of the preconceived ideas which we have inherited from the bacteriology era and let us be more open-minded to new findings. Above all, let us be factual and persistent in our search for the truth. Let us recognize our own shortcomings before we speak ill of a certain test. Let us try to judge things in their real perspective. Let us realize that with an extremely small sample (42 guinea-pigs and a dozen sera) Mr. McEwen's report does not disprove or discredit our work in this field or the supporting evidence reported by Dr. Burrows. Our work entails thousands of cases and long years of specific effort (we might add thousands of guinea-pigs and sera). This weight of evidence should have been an indication to Mr. McEwen and his advisers that something was basically wrong with their system.—I am, etc.,

JACK G. MAKARI.

Muhlenberg Hospital,
Plainfield, New Jersey,
U.S.A.

REFERENCES

1 Makari, J. G., *Brit. med. J.*, 1955, **2**, 1291.
2 —— ibid., 1958, **2**, 358.
3 —— *J. Amer. geriat. Soc.*, 1959, **7**, 611.
4 Burrows, D., *Brit. med J.*, 1958, **1**, 368.
5 Makari, J. G., unpublished.
6 Kulka, A. M., *J. Immunol.*, 1943, **46**, 235.
7 Trapani, I. L., Garvey, J. S., and Campbell, D. H., *Science*, 1958, **127**, 700.
8 Chase, M. W., in *Bacterial and Mycotic Infections of Man*, edited by R. J. Dubos, fifth impression, 1948. J. B. Lippincott Co., Philadelphia, p. 115.

Behind the Depressive Symptom

SIR,—Your annotation on the above subject (*Journal*, November 14, p. 1012) sets forth a number of highly debatable statements. In your description of "recurrent psychotic depression," you state that "it runs a limited course, and if suicide can be prevented the patient makes a complete recovery." You further state: "In this syndrome there is typically a positive family history, or a history of a previous attack or of excessive mood swings, insomnia with early-morning waking, anorexia, feelings of guilt and hopelessness, and retardation or agitation." Further on you state: "The same type of psychological stress can also cause neurotic depression, but the retardation and suicidal impulses are absent."

Your first statement is clearly not the experience of most psychiatrists. Prior to the introduction of electroplexy, the wards of most mental hospitals were cluttered with depressed patients, many of whom had spent years in acute or chronic depression, with no sign of "making a complete recovery." Many of these patients had had previous attacks from which they had recovered in the most varying periods.

(Where no dementia was present, electroplexy cleared up the vast majority of these cases in a few weeks.)

I have no fault to find with your clinical description of this syndrome, except that it must surely be very rare for a patient to wait until he could exhibit all these signs and symptoms before presenting himself for treatment. And, with 45% of all hospital beds occupied by mental patients, is a "positive family history" any longer of any value? But the last of your statements which I have quoted is by far the most controversial. Is there really such a thing as "neurotic depression" which will never become sufficiently deep to lead to suicidal impulses? Personally, I don't think there is, and I think he is a very brave psychiatrist who makes such a diagnosis. I do not think it can be too often stated that sustained depression of any degree means a *breakdown* (which of course one may call a "neurosis" purely as a euphemism), and is one of the cardinal symptoms of that breakdown. The other two cardinal symptoms, which may or may not be present, are tearfulness and disturbed sleep.

In my experience, all the difficulty both in diagnosis and treatment of these conditions is due to confusing the "distress" of anxiety hysteria with the depression of real breakdown. In anxiety hysteria (in my opinion, the only true neurosis) careful examination soon reveals that there is no real depression present. Nor are either of the other two cardinal symptoms ever present. I regard an immediate, precise diagnosis in these conditions as of fundamental importance in psychiatric practice. In my experience, many mildly depressed patients will quickly become suicidal. But also, in my experience, the mildest degrees of depression yield as dramatically to electroplexy as the more advanced cases. Electroplexy given in anxiety hysteria only of course makes matters worse, but the latter condition should yield almost immediately to correctly given counter-suggestion.—I am, etc.,

Pinner, Middlesex. ROBERT THOMPSON.

Gangrene after Intramuscular Chlorpromazine

SIR,—Dr. R. J. Hamer Hodge's contribution (*Journal*, November 7, p. 918) underlines the dangers inherent in intramuscular injections by nursing staff. Correct technique should exclude all dangers except where the drug preparation is particularly cytotoxic. It is all very well to consider some areas "safe," but even in my short professional experience I have seen fat necrosis from "intramuscular" iron, muscle necrosis from paraldehyde, sciatic-nerve damage from both chlorpromazine and tetracycline, and radial nerve damage due to antitetanus serum. Pity the poor nurses, but for heaven's sake train them to give intramuscular, indeed all, injections intelligently. I have seen a nurse, taught vaguely to inject only into the anterior aspect of the thigh, go dangerously close to the saphenous opening. It is generally recognized that the vastus lateralis muscle is a safe area, but I know a medical man who is very scathing in his criticism of the use of *his* vasti for a prolonged penicillin course. But better a few weeks' discomfort to a lifetime's foot-drop.—I am, etc.,

Southsea, Hants. W. J. O'CONNELL.

Osteomalacia in Asian Immigrants

SIR,—In view of the increasing number of immigrants from the Far East who cannot speak English, may I request your readers to bear in mind the possibility of osteomalacia when treating Asian women after confinement? Osteomalacia is endemic among the rice-eating people of Bengal and East Pakistan, and is relatively commoner among women between the ages of 20 and 30. It is not limited to the poorer classes, and the Moslem custom of purdah (secluding women from the sight of strangers) has been held to be responsible for its incidence among the middle and upper classes. Even in India the disease is not often recognized until far advanced.

The patient, usually after the third or fourth confinement, complains of pain of an aching type in the pelvic and sacral regions increased by movement and marked general weakness. In the later stages palpitation may be complained of and fever may be present. Sooner or later secondary anxiety symptoms may blur the clinical picture and the patient may be erroneously referred to a psychiatrist.—I am, etc.,

Belmont Hospital, Sutton. M. N. PAI.

Personal Medical Records

SIR,—In Tasmania we felt that it was time our citizens, in this 350,000-strong State of the Australian Commonwealth, had some form of record card similar to the soldiers' A.B.64, for the security of the individual and the assistance of the doctor. With the co-operation of the B.M.A., the approval of a Commonwealth Ministers for Health Conference, and the blessing of the Commonwealth National Health and Medical Research Council, we designed the personal medical information card whose four pages are here reproduced. In the near future we hope to have neatly fitting transparent, polythene envelopes, which the public can purchase cheaply and in which they can preserve their cards.

PERSONAL MEDICAL INFORMATION RECORD

Own Name .....Own Telephone No.....

Own Address .....

Name of Next of Kin.....Telephone No. of Next of Kin.....

Address of Next of Kin .....

Date of Birth ..... Blood Group ..... Rhesus Blood Group (Female Only) ..... Volunteer Blood Donor Number.....

N.B.—PLEASE STRIKE OUT CLEARLY AND CAREFULLY THE INAPPLICABLE INFORMATION IN THIS SPACE BELOW :—

I. I SUFFER FROM—1. EPILEPSY.
2. DIABETES.
3. HAEMOPHILIA (BLEEDING IS DIFFICULT TO STOP).

II. I AM SENSITIVE TO THE FOLLOWING ANTIBIOTIC OR OTHER DRUGS .. .. 1.....
2.....
3.....

III. I AM A VOLUNTEER "EYE DONOR." IN THE EVENT OF MY DEATH, PLEASE TELEPHONE THE ..... HOSPITAL AND INFORM THE SUPERINTENDENT.

ANY OTHER NOTES

Subject ..... | Remarks .....

Page 1

RECORD OF EXPOSURE TO X-RAYS, OR OTHER IONIZING RADIATIONS

YOUR DOCTOR OR RADIOLOGIST WILL ASSIST YOU TO RECORD THIS INFORMATION

Date	Type of Radiation: X-Ray Gamma &c.	Part of Body Exposed	Amount or Duration of Exposure	Date	Type of Radiation: X-Ray Gamma &c.	Part of Body Exposed	Amount or Duration of Exposure

If and when these spaces become fully used up copy the columns and lines on to a piece of paper of the same size, affix this down one side and use it as a continuation record sheet.

Page 2

IMMUNISING AGENTS Name .....

Address .....

Name of Agent	No. of Injections	Date of Administration	Name of Agent	No. of Injections	Date of Administration	Name of Agent	No. of Injections	Date of Administration
Salk Vaccine	1st		Diphtheria Toxoid	1st		Combined Anti-Diphtheria and Whooping Cough Antigen	1st	
	2nd			2nd			2nd	
	3rd			3rd			3rd	
	Booster			Booster			Booster	
Triple Antigen	1st		Combined Tetanus Toxoid and Diphtheria Toxoid	1st		Tetanus Toxoid	1st	
	2nd			2nd			2nd	
	3rd			3rd			3rd	
	Booster			Booster			Booster	
Other	1st		Other	1st		Other	1st	
	2nd			2nd			2nd	
	3rd			3rd			3rd	

Page 3

EARLY PROPHYLACTIC AND TREATMENT ANTI-SERA

Name of Agent	No. of Injections	Date of Administration	Name of Agent	No. of Injections	Date of Administration	Name of Agent	No. of Injections	Date of Administration
Diphtheria Anti-toxin (Prophylactic)			Tetanus Anti-toxin (Prophylactic)			Other		
Diphtheria Anti-serum (Treatment)			Tetanus Anti-serum (Treatment)			Other		

IMMUNISING VACCINATIONS (OTHER THAN "SALK")

Name of Agent	Date of Vaccination	Positive Response or Immune Response	Name of Agent	Date of Vaccination	Response	Name of Agent	Date of Vaccination	Response
Anti-Smallpox (Calf lymph)			Anti-Tuberculosis, B.C.G.			Other		

Page 4

Rather than distribute batches of the cards themselves all over Tasmania to various centres in the hope that people would take one as required and have it completed, we distributed application coupons via council offices, doctors' waiting-rooms, and chemists. We also advertised the scheme widely in the newspapers and the advertisement contained an application coupon. We felt that this method of distribution of the cards would encourage people to treat them with more respect. At the same time, we supplied cards to some of the hospitals and to doctors who requested them for the purpose of completing them and issuing them to patients. We felt that about 10% of the population would be sufficiently interested to obtain cards forthwith and that, by repeated advertising and the gradual spread of interest in the scheme, possibly 30% would eventually request these cards.

The scheme was commenced in July, 1959. So far over 3,000 people have applied for cards directly; 32 doctors have distributed over 6,000 cards and approximately 2,500 cards have been distributed by hospitals. We estimate that about 11,500 people have been supplied with cards and it is considered that it is an encouraging start, considering that this is a new project.—I am, etc.,

J. EDIS,
Director-General of Health Services,
Tasmania.

Temporary Paralysis after Polio Vaccine

SIR,—In describing what happened to his child following vaccination, Dr. M. S. Sabour (*Journal*, November 14, p. 1021) might have been describing what happened to my child following vaccination with Burroughs Wellcome vaccine, the only difference being that the vaccinated arm (the left) was affected.

It has been suggested that in such a case a series of injections of the vaccine should subsequently be given starting with 0.1 ml. and working up to 1 ml. I am afraid I have not yet had the courage to do this.—I am, etc.,

London, S.W.19. N. H. BARLEY.

Carcinoma of Fallopian Tube

SIR,—I was interested to read Mr. Derek Jefferiss's report (*Journal*, November 14, p. 1002) of a case of primary carcinoma of the Fallopian tube. I have just had a similar case, the details of which I append.

A married woman, 53 years of age, well built and rather obese, was admitted from casualty with a history of five days' abdominal pain and symptoms of intestinal obstruction, having previously been perfectly well. On examination a large mass was felt in the pelvis. Laparotomy revealed a large mass in the pelvis involving both ovaries, uterus, and sigmoid colon. Secondary deposits were found on the mesentery and on the bladder. As a palliative procedure oophorectomy, salpingectomy, and hysterectomy were performed and a transverse colostomy made.

Specimen.—The corpus uteri together with both Fallopian tubes and ovaries. The organ is 7.5 cm. long, 8 cm. wide, and 4.5 cm. thick. Both ovaries are cystic, and measure 9 cm. by 4 cm. and 7 cm. by 5 cm.

Microscopical Examination.—Sections from various positions show the lesion to be a primary carcinoma of the Fallopian tube with spread to the myometrium and to the ovary.

—I am, etc.,

St. Giles's Hospital, London, S.E.5. C. S. LYGONIS.

Tongue-tie

SIR,—Mr. Denis Browne's wise words and beautiful photographs (*Journal*, November 7, p. 952) should convince the many who still believe that "tongue-tie" is a myth. It is a very real and not so very rare congenital deformity.

Treatment of this has fallen into disrepute because in the past the normal fraenum of the tongue has been divided when there was absolutely no indication for it. This was done, I think, owing to a misunderstanding and a failure to realize that there is a dual meaning for the words "tongue-tied." First there is the physical one, meaning that the tip of the tongue is tied down to the back of the lower jaw by a tight congenital band; and, the second, an abstract meaning and an expression in common usage in the English language, referring to someone who cannot express himself adequately or at all.

In the past many parents thought that, if their child did not speak at the time they expected it to, its tongue was tied. If, therefore, it was untied it might then be able to speak. The surgeon or midwife in the old days sometimes also fell into this trap. The ancient practice of "snipping the tongue" to make a child speak is now well recognized as barbarous. But the pendulum has swung too far, and many go as far as to say "tongue-tie" does not exist, when it does. However, when

present, it only causes a minor defect in articulation, and often some difficulty in feeding. A severe defect in speech, or very late acquisition of intelligent speech, is most often due to subnormal or retarded mental development, for which division of a normal fraenum of the tongue is a forlorn method of treatment.

Treatment of a truly tongue-tied baby, whose fraenum is short, is now often neglected. These babies can be seen nearly every week in the out-patient department of any big hospital. The degree of disability is variable and debatable, but not the existence of the deformity. Although in the past all my patients who have suffered from this condition have been small babies,[1] recently a young man aged 22 came to me because he was tongue-tied. This interfered with the pronunciation of certain consonant sounds, especially "D" and "T," and he asked me to free his tongue. I freed his tongue and his disability disappeared. If his short fraenum had been divided when he was a baby, he could have been saved unnecessary embarrassment at school and in his work afterwards. The fact that he found this deformity troublesome should be a guide to parents and help them to decide that a small operation is necessary, although disability may not be apparent in a small baby unless it has had feeding difficulties.

Perhaps, as we cannot or would not alter the English language, it might be wise to sacrifice with sadness the simple Saxon description of the congenital defect and call it a "short fraenum of the tongue."—I am, etc.,

Leeds, 1. MICHAEL C. OLDFIELD.

REFERENCE

[1] Oldfield, M. C., *Lancet*, 1955, **1**, 528.

New Sulphonamides

SIR,—I read with interest the letter by Dr. A. Crowcroft (*Journal*, October 24, p. 826) on the successful use of prophylactic sulphonamide in controlling the spread of bacillary dysentery infection in a mental hospital ward. He rightly emphasizes the administrative problems involved when infection occurs in overcrowded wards now inconvenienced in many hospitals by internal alterations and modernization.

I can confirm the value of prophylactic sulphonamide in limiting the spread of dysentery infection in mental hospital wards. After experimenting with streptomycin administered prophylactically without success in June, 1958, we were faced with the problem of 27 cases of *Shigella flexneri* Type Z dysentery occurring in seven female wards with a total population of 600 patients—all possible contacts due to temporary cross-sleeping arrangements. The potential spread was fearful to contemplate, and every one of these patients was given a daily prophylactic dose of 0.5 g. phthalylsulphathiazole continuously over a period of two to three months. No toxic reactions were encountered and no more cases of dysentery occurred. The period of chemoprophylaxis was probably prolonged unduly, but I had in mind the danger from the subclinical case and the intermittent excreter.

In January, 1959, two patients with a history of previous attacks of dysentery developed a recurrent attack after transfer to a geriatric infirm ward. Prophylactic tablets were given and no new cases occurred. In March, 1959, two dysentery excreters were detected during a routine examination of old cases, and prophylactic tablets were again exhibited and no acute cases developed. In July, 1959, a female patient in one of the seven wards mentioned developed acute dysentery (first attack) and tablets were given to 80 contacts. No other case occurred.

I am of the opinion that, when dysentery is endemic in closed populations, prophylactic sulphonamide is effective in limiting the spread of infection, but periodic stool examinations are necessary to detect the intermittent carrier state. It is of interest to speculate whether the newer, long-acting sulphonamides such as sulphamethoxypyridazine successfully used by Dr. Crowcroft offer any advantage over the older drugs, but my experience certainly shows that phthalylsulphathiazole can be given over a long period of time without apparent harm, and is effective in protection against Flexner dysentery. And this confirms the report of Ross,[1] who successfully used the drug for the control of Sonne dysentery in a residential nursery.—I am, etc.,

Middlewood Hospital, Sheffield. F. T. THORPE.

REFERENCE

[1] Ross, A. T., *Med. Offr*, 1954, **91**, 95.

When to Tie the Cord

SIR,—To support Dr. A. E. Chisholm's theory in his letter (*Journal*, October 17, p. 759), I can add the experience of seeing embolic gangrene of the leg in a neonate, when the nurse was in the habit of aiding the return of cord blood to the baby before tying the cord.

I took the day-old child with a white, "dead leg" to the late Mr. Hobill Cole, then senior surgeon, Melbourne Children's Hospital, who told me this was no uncommon case and was due to the temporary patency of the ductus arteriosus (in all normal babies) allowing systemic embolism rather than pulmonary infarcts. Whether embolectomy (unknown in 1918?) would have saved the leg (and others) in these modern times is problematic. But don't invite it. Tie early, and—an old tip still useful—to avoid bleeding from umbilical arteries as the jelly of Wharton slowly shrinks, use silk-covered, round hat-elastic—three or four ties of the 2- or 3-mm. thick stuff. Far safer than linen-thread. About 5% of babies have a long process of their own skin along the cord, and in that type at one time I used to tie the elastic flush with the abdominal wall. The final result was a practically navel-less child, very neat, but the cord was a little slow to separate. The slight possibility of enclosing a bit of gut or bladder, and the need to watch the stump for at least 14 days, made me desist after doing a hundred or so cases, but perhaps the method could be modernized, so as to prevent hernia in later life.—I am, etc.,

Bishop's Stortford, Herts. R. A. R. WALLACE.

Syphilis and Mental Deficiency

SIR,—While it is true, as stated by Dr. J. D. Redmill (*Journal*, October 17, p. 759) and by Dr. G. L. M. McElligott (*Journal*, October 31, p. 888), that a number of cases of venereal disease are treated privately or otherwise than at the usual clinics, mental deficiency due to syphilis tends to show itself at an early age, and such patients are therefore admitted for investigation to a children's unit or to a special hospital. In my experience over a number of years at the Lock Hospital, and at Queen Mary's Hospital, Carshalton, it was a relatively small proportion of congenital syphilitic children showing mental defects that were admitted to the hospitals. Such cases always manifested themselves by backwardness in general development, and especially inability to sit up by the age of 2 years. It is of interest to note that these children (according to my

records) usually gave a negative Wassermann reaction in the blood but a positive reaction in the cerebrospinal fluid.

In view of this consistent finding it is, of course, possible that some cases were referred to an institution for mental defectives rather than to a special V.D. children's unit, since they showed few, if any, other signs of congenital syphilis. Nevertheless, I would wish to support the findings of Drs. J. M. Berg and B. H. Kirman (*Journal*, September 12, p. 400) that the number of mentally deficient children whose deficiency is due to syphilis is very small.—I am, etc.,

London, W.1. G. M. SANDES.

"No Connexion Whatsoever"?

SIR,—Whatever differences of opinion you and I have about the value of injections against influenza, there is no room for any doubts about the inaccuracy of your statement that the Institute of Directors organized last week a conference for its members on the dangers of high-pressure living. This conference had no connexion whatsoever with the Institute of Directors; it was organized in fact by the Chest and Heart Association, and I would have thought that you might have been aware of this. Thus your somewhat tasteless suggestion that the programme should include a session on high-pressure advertising should have been addressed to the Chest and Heart Association and not to the Institute of Directors. I cannot speak for the Chest and Heart Association, but I presume that they will treat it with the contempt which it deserves.

The circulation to the press of the photograph which you reproduce was due to a misunderstanding between the firm concerned and myself. If I had known that the intention was to circulate generally such a photograph, my knowledge of medical etiquette is sufficient to have any personal reference deleted.

Only time and trial will test whose views are correct on the efficacy of influenza injections and the possibility of an epidemic. I have sufficient confidence in my opinion to believe that you are mistaken.—I am, etc.,

Institute of Directors, London, S.W.1. H. BERIC WRIGHT.

*** We did not state that the Institute of Directors organized the conference held in Festival Hall last week. We wrote (*B.M.J.*, November 21, p. 1077), "The Institute of Directors is having a field-day . . . ," erring, perhaps, in the direction of euphemism. Lord Baillieu, distinguished chairman of the Dunlop Rubber Company, presided over the morning session. The afternoon session was presided over by Sir Richard Powell, director-general, Institute of Directors, who in his "message" printed in the programme states that ". . . over a year ago, we set up a research unit to investigate the medical problems of business life." And he continues thus: "That such a distinguished body as the *Chest and Heart Association* should join us in this field is gratifying and most encouraging, and I should add that, personally, it gives me particular pleasure to be associated with this most excellent new venture into health education." The words "join us" and "associated with" suggest some sort of connexion—"whatsoever."—ED., *B.M.J.*

Service Psychiatrists

SIR,—The recent letters by Dr. J. F. Wilde (*Journal*, November 7, p. 953) and Dr. W. A. Lethem (*Journal*, November 21, p. 1101) on behaviour during bombardment prompt this personal reminiscence.

During the last war I was medical officer to a tank battalion in the Western Desert. We were frequently bombed and machine-gunned from the air, and during these attacks we would dive into slit trenches or hastily climb into tanks for shelter. This was routine practice in which all (including the colonel, D.S.O. and bar, and M.C.) participated. During one of these attacks a driver who had been delivering my medical supplies from a field ambulance was present. He was urged to take shelter but did not, and merely stood on the edge of a slit trench gazing down at the crouching occupants with a patronizing smile. I was much impressed with this man's indifference to danger and determined to try to get him transferred as my dresser. With this in mind, I drove over to the field ambulance a few days later to make tentative inquiries, but, alas, I learned he had been evacuated to a base hospital suffering from schizophrenia.—I am, etc.,

London, W.5. S. LASK.

*** This correspondence is now closed.—ED., *B.M.J.*

Phenoxymethylpenicillin and Drowsiness

SIR,—For the past 18 months I have been puzzled by an apparent soporific effect of treatment with phenoxymethylpenicillin. It was in particular brought to my notice in four cases which were on long-term maintenance doses. Two were elderly bronchitics who were receiving aminophylline in one case, and aminophylline and digitalis in the other. The other two cases were of recent rheumatic fever in children about 14 years old, and were at the time receiving no other drugs. The dosage was 125 mg. a day, and reduction or omission of the dose resulted in return to normal wakefulness. Several patients with acute infection have remarked upon feeling sleepy when taking the drug, but may have been affected in fact by the disease.

I am curious to know if any other of your readers have had this experience. I have not noticed it occurring with other forms of penicillin.—I am, etc.,

London, S.E.13. W. M. C. HALLINAN.

German Medicine Abroad

SIR,—The interesting letter from Professor W. C. W. Nixon (*Journal*, October 10, p. 693) touches on a matter which is of importance outside of south-east Asia. It is interesting to note that here and in other places along the West Coast of Africa, with which I have contact, there is an increasing tendency for the British doctors to be homeward bound, and for their places to be taken by Italian, Dutch, German, and Swiss doctors. My experience in meeting these newcomers is that they are alert, very well trained, and enthusiastic. Many come from well-known universities whose reputation is certainly upheld by their representatives.

It is distressing to see this change, however. With our record in the field of tropical medicine, it is a shame to leave the developed field empty. It does not seem to have occurred to the young men at home that the change of status in many of our former colonies has now transformed what was almost exclusively the Colonial Medical Service area into a much wider one for the freelance doctor. The prospect of adventure and the satisfaction of making one's own way are in a sense much greater than before. It is clear that our European colleagues are alive to the real situation, and

if our young men are really lacking in spirit—which I do not believe for one minute—then British medicine will surely slide into the background.—I am, etc.,

Navrongo, Ghana. A. T. ANDREASEN.

Combined Pethidine and Antagonists in Obstetrics

SIR,—We have read with interest Dr. John Bullough's paper (*Journal*, October 31, p. 859) on the use of premixed solutions of pethidine and narcotic antagonists for obstetrical analgesia. We also have had experience with a pethidine-levallorphan mixture in obstetrics. Prior to the use of the mixture we had considerable experience of the use of pethidine alone. On a few occasions, as is generally accepted, the infant showed evidence of respiratory depression which necessitated treatment. Since using the pethidine-levallorphan mixture respiratory depression has not been observed.

Our experience, however, is not strictly comparable with Bullough's because we were using "pethilorfan," which contains pethidine and levallorphan in the proportion of 80:1, whereas he was using a proportion of 50:1. We were therefore interested to study his results to find out whether, with a somewhat higher proportion of levallorphan, there was some loss of the analgesic activity of the pethidine. Bullough comments, "As confidence in the method of using premixed drugs grew, an increasing dosage was used, providing better analgesia for the mothers, without any corresponding increase in the incidence of neonatal asphyxia." At first glance, his Table I appears to bear this out. However, closer study shows that, in Series A, the figures given for percentage "good," "fair," and "unsatisfactory" analgesia do not add up to 100. Could the author please correct these figures ?*

Dr. Bullough refers in his paper to findings in 2,000 women treated with pethidine/levallorphan, in the proportion of 80:1. May we please know whether he found this more or less effective than the 50:1 proportion ?—We are, etc.,

Maternity Hospital, Cambridge OSWALD LLOYD. JOHN A. CARRON BROWN.

*Dr. Bullough informs us that there was, unfortunately, a typing error in his Table I. The relevant part of the Table should have read:

	Series			
	A	B	C	D
Drugs used for each injection† (mg.)	P. 100	P. 100 N. 2	P. 100 N. 5	P. 100 L. 2
Analgesia produced according to patient's reply next day:				
Good (%)	58	66	76	76
Fair (%)	36	29	19	21
Unsatisfactory (%) ..	6	5	6	3

† P. = Pethidine; N. = nalorphine; L. = levallorphan.

Behaviour of the Market Place

SIR,—Your leading article on "Behaviour of the Market Place" (*Journal*, November 7, p. 937) is most timely. Having seen medical men displaying their wares on television, one wonders how much we differ from the gentry in market places with their quack cures.

It is not surprising that the *Daily Telegraph* has recently referred to the doctors' claim for a "wage increase." We shall soon be admitted to our patients' houses via the tradesmen's entrances and will only have ourselves to blame.—I am, etc.,

Epsom. E. N. CALLUM.

Obituary

H. W. WILSON, M.S., F.R.C.S.

Mr. H. W. Wilson, consulting surgeon to St. Bartholomew's Hospital, died at Bungay, Suffolk, on November 14. He was 79 years of age.

Harold William Wilson was born at Carlisle in 1880. He received his medical training at St. Bartholomew's Hospital, and qualified M.R.C.S., L.R.C.P. in 1903, in which year he gained the Matthews Duncan exhibition for midwifery and diseases of women. He followed this award with the Brackenbury scholarship in surgery and the Willett medal in operative surgery in 1905, the year in which he was admitted a Fellow of the Royal College of Surgeons of England, and in 1906 he was awarded the Luther Holden scholarship in surgery. In the following year he obtained the London degrees of M.B., B.S., proceeding to the M.S. in 1909. In the years immediately after qualification he held a number of appointments at St. Bartholomew's Hospital, ranging from junior house-surgeon and junior demonstrator in anatomy to chief assistant surgeon in the out-patient department and senior demonstrator in anatomy. Later he became surgical registrar, full surgeon, joint lecturer in surgery, and demonstrator of operative surgery at the hospital, and, ultimately, consulting surgeon. He served a term as president of the Abernethy Society. In the early years of his career he was also clinical assistant at St. Peter's Hospital for Stone, surgeon to out-patients at the Victoria Hospital for Children, and assistant surgeon to the Royal Cancer Hospital. He also became consulting surgeon to the Woolwich and Plumstead, the Potter's Bar, and the Leatherhead cottage hospitals. In collaboration with Dr. C. M. Hinds Howell he wrote a book entitled *The Movable Kidney: Its Pathology, Symptoms, and Treatment*, which was published in 1908. He was joint editor, with the late Professor G. E. Gask, of *Surgery*, a textbook by various authors which was published in 1920, and to which he contributed the article on surgery of the urinary and male genital systems. During the first world war he served in France as a surgical specialist in the R.A.M.C., attaining the rank of major.

Mr. R. FOSTER MOORE writes: Harold Wilson was one who, from the first, set out to be a surgeon, and for judgment, wisdom, and technical skill he was destined to become one of the outstanding surgeons of his time—one to whom so many of his colleagues came in case of personal need. After qualifying he was appointed demonstrator of anatomy at St. Bartholomew's under Dr. Addison (later Lord Addison) who had just been elected to the newly established chair of anatomy. At this period it was almost essential to have served as demonstrator in one of the preclinical studies in order to be appointed to the clinical staff of the hospital, and when the vacancy arose he became assistant surgeon to Cozens Bailey.

In his early days he developed a leaning to urinary diseases and published a book on the movable kidney in conjunction with Dr. Hinds Howell, but his most important contribution was the well-known textbook on surgery written in conjunction with George E. Gask. During the busiest period of his life he suffered badly from gastric trouble, which restricted his activities. After suffering for many years from what was a distressing disability, he submitted to operation, and from this he derived such benefit that he was able entirely to dispense with serious dieting.

He was one upon whom the weight of two wars fell. During the first, he worked for a time in France as surgical specialist to a base hospital at Boulogne, returning later to St. Bartholomew's to help the much-depleted staff. He was a good teacher, and no one who acted as his dresser will fail to recall his benevolent and solicitous—"My dear . . . , don't be such a b . . . f . . ." In the second

world war he acted as superintendent over the resident staff there. After a time he found it too onerous to continue this work from his home in Harley Street, and so, with his greatly devoted wife, migrated to the upper part of a small house in Charterhouse Square from which he was on call at all hours, day or night, blitz or no blitz. And there he remained to the end of the war, a heavy strain on a not-too-robust constitution, and an exhausting experience for his wife.

He was essentially an outdoor man: a skilled fisher, a keen and, I am told, an excellent shot, and an enthusiastic motorist; at one time he played the violin. With the intent of having a week-end resort and a place to which they might ultimately retire, he and Mrs. Wilson built a pleasant house on Herringfleet Hills, near St. Olaves, in up and down heather and woodland. It was perched on a bluff with a wide uninterrupted view of the Broads, and here they entertained their friends and enjoyed country life. It was here that Hester died suddenly, a most crushing blow from which he never recovered. I believe it may be said, with greater probability than is sometimes the case, that they both were victims of the war. One daughter, Mrs. St. Leger Moore, survives him.

Mr. F. C. W. CAPPS writes: With the passing of Harold Wilson within a few weeks of his 79th birthday we have lost yet another of the dwindling group of surgeons who served Bart's from the first world war until the end of the second conflict. He was also for many years consulting surgeon to Leatherhead and Potter's Bar cottage hospitals in the days when such appointments meant many a midnight journey for emergency abdominal and other work. In 1914–18 he served in France and at the 1st London General at Camberwell with the rank of major. There were few high ranks among the R.A.M.C.(T.) in those days. He was appointed to the staff of Bart's in 1918 and became assistant surgeon to Mr. (later Sir) Holbert Waring. This was a great firm of contrasting personalities. Most of the night emergencies became his province, and he never failed to come down at his house-surgeon's behest. He became senior surgeon to the hospital in 1936. At the outbreak of the second world war he was posted to Hill End Hospital, but was happier when he returned to London and to the surroundings of his beloved Bart's. Due to retire in 1941, he, with others, stayed on at the governors' request, and only left the active staff in October, 1945. He took up residence in Charterhouse and stuck out all the air raids, giving calm and loyal service and doing much of the emergency and casualty surgery night and day. When it is remembered that for most of his life on the staff he was considered a somewhat delicate man—he suffered from a duodenal ulcer—this was a magnificent record, and only after retirement did he seek surgical relief, and gained greatly by it. His surgery, outstanding in the great days of general surgery, was meticulous and gentle, and he displayed fine judgment and humanity. With perhaps a leaning towards genito-urinary work, he nevertheless did fine breast, abdominal, and rectal work, and took endless pains over the fractures which fell to the general surgeon of those days. His results in all he did showed an unusually high percentage of success, and his experience was enshrined in Gask and Wilson's *Surgery*, which he edited. Never a great committee man, he did not take much part in the administrative work of the medical school, but as a teacher he was unsurpassed. After his work, his great joy was in country pursuits, especially shooting and fishing. It was sad that his retirement to the country house in Norfolk, in the building of which he and his wife spent so much loving care, was saddened for him by her death only a few years after they had taken permanent residence there. Henceforward living alone, he became more and more reserved and cut off from his friends, and was rarely seen in London. This was a great loss to the many who loved and admired him and who would have liked to see more of him in his old age. His only child, a daughter, now married and with a family, survives him, and to her we tender our sympathy in the loss of a father who was revered by many colleagues and who earned the gratitude of countless patients.

Sir FRANCIS PRIDEAUX, C.B.E., M.R.C.S., L.R.C.P.

Sir Francis Prideaux, formerly director-general of medical services of the Ministry of Pensions, died at Queen Mary's Hospital, Roehampton, on November 15. He was 75 years of age.

Joseph Francis Engledue Prideaux was born on March 13, 1884, the son of Dr. T. E. P. Prideaux, of Wellington, Somerset, and was educated at Epsom College and at University College, London, qualifying M.R.C.S., L.R.C.P. in 1908. In the following year he entered the Colonial Medical Service, and was a Government medical officer in Fiji until 1916, when he returned to England to enter the R.A.M.C. for service in the first world war. In 1921 he was invited to join the medical staff of the newly created Ministry of Pensions, and was given specialist duties at headquarters. During the war he was able to give close study to the problem of nervous disorder in all its aspects, particularly that of "shell shock," and he continued this study in his Ministry appointment. The Ministry was faced with the many difficulties in the diagnosis and treatment of the thousands of cases of "neurasthenia" which had emerged from the war. He approached the problem as a psychiatrist, and his methods proved highly successful. In April, 1936, he was appointed a member of an inter-departmental committee set up by the Home Secretary, the Minister of Health, and the Secretary of State for Scotland "to inquire into the arrangements at present in operation with a view to the restoration of the working capacity of persons injured by accidents, and to report as to what improvements or developments are desirable, and what steps are expedient to give effect thereto, regard being had to the recommendations made in the report issued by the British Medical Association in February, 1935, on fractures." The inter-departmental committee issued an interim report in June, 1937. Soon after the outbreak of the second world war in 1939 he was made a director of medical services in the Ministry of Pensions, and in 1942 became deputy director-general. He succeeded the late Sir Walter Haward as director-general in 1947, and held office until he retired in 1949. Appointed O.B.E. in 1941, he was promoted C.B.E. five years later, and in 1949 was created a knight. He married Miss Lucy R. Clive in 1910, and she survives him together with the two daughters of the marriage.

F. T. R. writes: Sir Francis Prideaux will be remembered by his old colleagues in the Ministry of Pensions with warm affection and esteem. His qualities of heart no less than of mind endeared him to all who had the privilege of working with him. He was not only a great chief but also a generous and trusted friend. His ready help and encouragement was an inspiration to his staff, and his wise advice was always available to any medical officer beset by a problem, official or otherwise. His abounding good humour and his fund of reminiscences—especially of his seven years as a medical officer in Fiji—made him a delightful companion who could while away the tedium of the longest journey or enliven the dullest occasion. Tall and of fine physique, he was a keen athlete in his student days and was a formidable front-row forward in the U.C.H. rugger side. Among his many interests was Freemasonry, in which he had held many offices.

Prideaux's outstanding work on neurosis and psychiatry between the two wars is well known. In the autumn of 1939 he took over the direction of the Ministry's hospital services, which had to be rapidly extended to meet the ever-increasing demand. This urgent and exacting task provided full scope for his great administrative ability. His achievements were many, but, in particular, his name will be associated with the building of Stoke Mandeville Hospital as a spinal injuries centre, and with that bold adventure in the rehabilitation of the paraplegic, the Duchess of Gloucester House at Isleworth.

Prideaux had a receptive mind open to new ideas and new methods. He encouraged research in every possible way, especially into design and construction of artificial

limbs and appliances. After his retirement in 1949 he maintained his connexion with Queen Mary's Hospital, Roehampton, by joining the Board of Governors. In spite of the long journey from his home, he rarely missed a meeting. He was blessed with a very happy home life, and those of us who were his contemporaries in the old Ministry will wish to extend our deep sympathy to his devoted wife and family.

E. S. HORNING, M.A., D.Sc.

Professor Eric Horning, professor of experimental pathology (histopathology) in the University of London, died suddenly on November 14. He was 60 years of age.

Eric Stephen Horning was remarkable in many ways. In the first place his title, professor of experimental pathology (histopathology) in the University of London at the Institute of Cancer Research, Royal Cancer Hospital, was unique in itself. He had travelled a great deal and had carried out research in many institutions in three continents, and had visited the other continents on numerous occasions. He had served in the Army in Europe during the first world war, and in the Royal Air Force and the Royal Naval Volunteer Reserve during the second world war. He was a man with great zest for life, of which he had enormously varied experience.

He was born at Sydney, New South Wales, and was educated at Barker College. His studies were interrupted when at the age of 16 he joined the Army and saw active service during the war in France. After the war he went to Oxford, where at Hertford College he took his B.A. in the honours school of comparative anatomy and zoology in 1924. He then returned to Australia to pursue research in the department of zoology in the University of Melbourne, where he was awarded the degree of D.Sc. in 1928. He held a Rockefeller fellowship for medical research from 1930 until 1933, during which time he worked with Dr. Albert Fischer in Berlin, with Dr. Alexis Carrel in New York, with Dr. E. V. Cowdry in St. Louis, and also in Paris and Prague. During this time he had worked on cellular histology, and his research on the enzymatic function of mitochondria was much in advance of the ideas of the time. He started cancer research in 1933, having been awarded a Beit memorial fellowship to work at the Imperial Cancer Research Fund laboratories. His first investigations in London were on the effects of radiation on normal and tumour cells, using micro-incineration to determine the distribution of "inorganic radicals" within the cell. Up to within a few hours of his death he was working on this problem in connexion with the distribution of iron in tissues of animals in which cancer had been induced with iron dextran and other complexes. Horning was appointed to the staff of the Imperial Cancer Research Fund in 1937, and with Dr. W. Cramer began to study the endocrine aspects of cancer. He became an expert in this field, and the book *Oestrogens and Neoplasia*, written jointly with Harold Burrows and published in 1952, is still of very great value.

Horning served in the R.A.F. from 1939 until 1941, when he was invalided out. In 1942 he was sufficiently recovered to volunteer for the Royal Navy, and served first at Greenwich, then with Naval intelligence in Iceland, South Atlantic waters, and finally in the Far East. He was released from the Navy in 1945 with the rank of lieutenant-commander, and returned to the Imperial Cancer Research Fund. He joined the staff of the Chester Beatty Research Institute in 1947 and was appointed professor in 1956. Eric Horning was always dedicated to service, to his country, to his laboratory, to his many friends, and to sick people in need of comfort and help. He had exceptional charm of manner, in speech and in writing; he was also a true connoisseur. As he was able to serve in the Army at the age of 16, he probably looked older than his real age at that time, but at the end of his life he had the appearance and spirit of a much younger man. His death is a great loss to many colleagues and friends.—E. B.

G. F. RAWDON SMITH, T.D., M.D., F.F.A. R.C.S.

Dr. G. F. Rawdon Smith, honorary consulting anaesthetist to Liverpool Royal Infirmary, died peacefully at his home at Berkhamsted, Hertfordshire, on October 30. He was 77 years of age.

George Francis Rawdon Smith was born at Madeley, Shropshire, on May 8, 1882, and was educated at Greenbank School, Liverpool, and at Rugby School, where he was the third generation of his family and where he was to be followed by his two sons. He began his medical studies at what was then the Liverpool College of the Victoria University of Manchester, and graduated M.B., Ch.B. from Liverpool University in 1907, proceeding to the M.D. in 1914. Meanwhile he had been to London to enter University College Hospital Medical School, and in 1911 he obtained the London degrees of M.B., B.S.

There may be old students of University College Hospital who remember George Smith as referee on the rugby football field. An enthusiastic rugby footballer himself, he had led the scrum of the Liverpool University pack and was captain of the side in 1904–5. After returning to Merseyside from London he refereed the Birkenhead Park and Waterloo games for many years. George Smith specialized in anaesthetics, and was honorary anaesthetist to the Royal Infirmary, the Women's Hospital, and the Dental Hospital, all in Liverpool. He was lecturer in dental anaesthesia in the University of Liverpool, and his contributions to the literature included *Dental Anaesthesia*, written in 1926. There will be many who remember with gratitude not only his help in the operating theatre but also his share in the advancement of the art and science of anaesthetics. It was a compliment not only to himself but to all his specialist colleagues within the region that he was the first anaesthetist to be installed as president of the Liverpool Medical Institution. In 1935 he was one of the first to receive the Diploma in Anaesthetics of the English Royal Colleges, having been an original member of the body which drew up the regulations for the diploma, and in 1948 he was elected a founder Fellow of the Faculty of Anaesthetists of the Royal College of Surgeons of England.

In 1913 George Smith was gazetted lieutenant, R.A.M.C., T.A. He served in France and Italy in the first world war, and was mentioned in dispatches in 1916. His interest in the Territorial Army was to continue, and twenty years' faithful service brought the well-deserved Territorial Decoration in 1924, the command of the 16th Field Ambulance, and, finally, the rank of full colonel and the appointment of assistant director of medical services 55th Division. In the second world war he was a lieutenant-colonel in the Home Guard, and medical adviser to No. 1 zone in the West Lancashire area. After the Home Guard had been disbanded he ran a first-aid post at Liverpool Royal Infirmary and joined the medical service committee under Mr. K. W. Monsarrat. There are very many who not only admired his work and public service but enjoyed his friendship and loyalty. A member of the British Medical Association for nearly fifty years, he was chairman of the Liverpool Division in 1931–2. He leaves a widow and a son and a daughter, also a son and two daughters of his first marriage, to all of whom we offer our sympathy.—H. V. F.

KEITH WARBURTON, M.B., Ch.B.

Dr. Keith Warburton is presumed to have lost his life in July this year while mountaineering on the north-west frontier of Pakistan. He was 31 years of age.

F. J. D. writes: Keith Warburton graduated M.B., Ch.B. at the University of Liverpool in 1951, and during the next eight years managed to combine his medical career in paediatrics with a growing aptitude for mountaineering and exploration. Between house appointments in Liverpool and his National Service, he spent three seasons in South Georgia, the latter two as a member of the geographical survey led by Duncan Carse, when Shackleton's journey

was repeated and the island traversed. During 1957 he was a member of the expedition led by Alfred Gregory to climb Disteghil Sar in the Karakoram. In 1958 he obtained the D.C.H. of the English Royal Colleges. In July of this year he led a combined Anglo-German expedition to climb the highest unnamed peak in the Batura Mustagh area of the Karakoram range. Adverse weather conditions led to the five climbing members of the party being overtaken by snow and avalanche while high on the mountain, and their tragic deaths must now be presumed. His modesty, integrity, and sense of humour made him many friends, and with his love of nature and mountains his qualities may be said to resemble those of Scott's companion, Dr. E. Wilson. Keith often endorsed the latter's remark, "How much better this has all been than staying at home." The deepest sympathy of all who knew him goes to his widow and parents.

R. H. W.-J. writes: I first met Keith Warburton in 1955, when he came as my house-physician in the paediatric unit of Whiston Hospital. His quiet unassuming manner soon endeared him to both patients and staff. The first news of his disappearance came through on the radio, and within a few minutes a feeling of great sadness and personal loss quickly pervaded the whole unit. He was very fond of children and they responded to him in the way children will with people whom their natural instinct tells they can trust. He was extremely painstaking, careful, and conscientious in his work, basing his conduct on the principle that if a job was worth doing it was worth doing well. Whatever happened on that last journey, I know that it was not due to any oversight on Keith's part. His natural love of mountains was a thing which we ordinary mortals can never understand, but without men like him the world would indeed be a poorer place.

ANDREAS PLENK, M.D.

Professor A. Plenk, director and chief surgeon in the State Hospital, Linz, Austria, died on October 2. He was 67 years of age.

Sir GORDON GORDON-TAYLOR writes: The death of Andreas Plenk closes the career of an Austrian surgeon who made an important contribution to the surgery of the stomach in addition to all his other activities as director and chief surgeon in the State Hospital at Linz. Plenk was born at Odenburg in what was then Burgenland in August, 1892, and had just reached the age of 67 at the time of his death. I had enjoyed his friendship for many years: there may have been this bond, that we had each approached surgery along the now outmoded avenue of anatomy, for Plenk had been a favourite pupil of Tandler, the famous Vienna anatomist, and it was Tandler's strong support that sent him at an early age to the directorship of surgery at Linz.

Like his friend Hans Finsterer, he was a pupil of the famous Viennese surgeon, Hochenegg. Subsequently he taught in Denk's University clinic in Vienna, and was given the title of university professor in 1950. His particular modification of the resection-for-exclusion operation for irremovable duodenal ulcer, as championed by Finsterer, won the warm approval of Finsterer himself. Although I always spoke of the technique as Plenk's modification, as it is generally known on the Continent, there can be no doubt that Bancroft anticipated him by three or four years, but of course the American for long years failed to realize the necessity for simultaneous gastrectomy. His attributes as a distinguished surgeon and a charming Austrian gentleman brought him many honours in his own land and abroad. His wife, Dr. Isa Plenk, survives him.

J. FORD THOMSON, M.B., Ch.B., D.P.M.

Dr. J. Ford Thomson, Consultant Children's Psychiatrist to the Shrewsbury and Wolverhampton Hospital Groups, died at his home in Knockin, near Oswestry, on October 13. He was 48 years of age.

S. S. writes: After graduating at Edinburgh James Ford Thomson embarked upon a career in the Indian Medical Service, but it was not long before he had decided that his true vocation lay in the field of child guidance. During the second world war he served as a surgical specialist and then as officer commanding an Indian military hospital, but all his spare moments were devoted to extending his reading of psychology and to applying his original and critical mind to the problem of the maladjusted child. With the partition of India in 1947 and the disbandment of the I.M.S., the reputation he had already gained led to his appointment as adviser in child psychology to the Government of Madras. During the tenure of this appointment he not only framed a Children's Bill, based on a modern and humane approach to the delinquent and maladjusted child, but he was able to test his theories of child guidance with remarkable success. His great love for and understanding of children were coupled with a strong belief in the child as a personality.

In 1949 Thomson returned to England, and found that if he wished to continue with his work he would have to conform to the pattern laid down by the National Health Service. At considerable financial sacrifice, he began the task of "climbing the ladder" in psychiatry, and passed from registrar to S.H.M.O. and then to consultant, acquiring the D.P.M. on the way. During his period as S.H.M.O. in Derby he continued to have most extraordinary success with his child patients. All of them knew him as "Uncle Ford" and many of them called upon him at his home, where his devoted wife seemed regularly to repeat the miracle of the loaves and fishes. His transfer to the Birmingham Regional Hospital Board as consultant occurred at a time when he had experienced what subsequently proved to be the initial attack of disseminated sclerosis.

But Thomson devoted all his energies to his new field and worked unsparingly to build up the child-guidance service in his area. He became more than ever dedicated to his task, and, in the face of increasing disability brought on by succeeding attacks of his disease, was indomitable in his efforts to carry on. His success continued and he added to the numbers of children whose lives he transformed. His correspondence with his former patients grew ever larger, but he insisted on maintaining it and in welcoming all the children who came to see him. His wife had to act as his chauffeur, drove the long distances between his clinics, and assisted him into the wheel-chair in which he ultimately had to see his patients. It was only a short time before his death that he was compelled to abandon his duties, but to the very end his children were always in his thoughts.

Ford Thomson's success with children was something that seemed to owe little to the teachings of the schools. His death at such an early stage of his career has made it impossible to test whether he could, in fact, have founded a school of his own, but it is doubtful whether anyone without his own unique gifts of love and understanding could have carried on his work. He was a truly dedicated man whom many will mourn. Our deepest sympathy goes out to his widow and to his son, himself on the threshold of a career in medicine.

ELLEN M. FARRER, M.B., B.S.

Dr. Ellen Farrer, for many years physician to the hospital which bears her name at Bhiwani, in the Punjab, died peacefully at Rickmansworth, Hertfordshire, on October 15. She was 94 years of age.

Ellen Margaret Farrer was born in London on September 29, 1865, the daughter of the Rev. William Farrer, and was educated at the South Hampstead High School and at Bedford College, London. She studied medicine at the London School of Medicine for Women, and graduated M.B., B.S. from London University in 1890. After graduation she held the appointment of resident medical officer at the Elizabeth Garrett Anderson Hospital. She then went to India with the Baptist Missionary Society to Bhiwani, where she founded a hospital, at first in a primitive hut which had no doors and no windows. In her early days there she had to perform operations in the

open air because the hospital lacked adequate lighting. Another problem she had to face was how to gain the confidence of her patients, to whom the sight of a stethoscope or a thermometer gave cause for alarm. Dr. Farrer's kindness and gentleness eventually gained the day, and the number of her patients increased considerably; so much so that in 1908 she was given the help of a medically qualified assistant and a nursing sister.

During the first world war she came back to England on sick leave, and then held an appointment at the Rosa Morison House of Recovery, a branch of the Elizabeth Garrett Anderson Hospital, at Barnet. She returned to India in 1918, and for a year was a surgeon at the Lady Hardinge Hospital, Rajputana. In 1920 she returned to Bhiwani, where, three years later, a new hospital with fifty beds was built and named the Farrer Hospital in her honour. When Dr. Farrer finally left India in 1933 she brought back to England many tributes to her skill as a doctor, including an alabaster model of the Taj Mahal tomb on a marble base. This, and other mementoes of her life in India, she treasured until her death. Her services were officially recognized by the award of the Kaisar-i-Hind silver medal, and, in 1928, the Kaisar-i-Hind gold medal. During the second world war, although well over 70 years of age, she came out of retirement to help tend the sick and the wounded. Latterly she devoted much time to painting, and at the age of 90 could be seen boarding the bus from her home at Bushey to travel to Watford to buy the artists' colours she needed.

J. D. LOUDON, M.B., F.R.C.P.C., F.A.C.P.

Dr. J. D. Loudon, formerly assistant professor of medicine in the University of Toronto, died in Toronto on October 16. He was 78 years of age.

Julian Derwent Loudon was born at Toronto on May 27, 1881, the son of Professor James Loudon, the first Canadian-born president of the University of Toronto, in which he was for many years professor of mathematics and natural philosophy, and one-time president of the Royal Society of Canada. Julian Loudon was educated at the University of Toronto, where he graduated M.B. in 1906. After graduation he came to England for postgraduate study at the London Hospital, and took the London Conjoint diploma in 1908. He then held appointments as senior resident physician at the City of London Hospital for Diseases of the Chest and the Great Northern Central (now the Royal Northern) Hospital. He returned to Canada, and was a member of the teaching staff of the faculty of medicine of the University of Toronto from 1912 to 1945, except for a period of war service, and for the last eighteen years was assistant professor of medicine. During the first world war he served overseas as a captain in the Royal Canadian Army Medical Corps. He was chief physician to St. Michael's Hospital, Toronto, from 1921 to 1945, when he became consulting physician. Since 1915 he had been associate coroner for the city of Toronto, and for many years he was consulting physician to St. Joseph's and Queen Elizabeth hospitals in Toronto, and to the medico-legal branch of the office of the Attorney-General of Ontario. For some time he was associate editor of the *Canadian Journal of Medicine and Surgery*. In 1920 he was elected a Fellow of the American College of Physicians, of which he was also a life member, and in 1929 he was admitted a Fellow of the Royal College of Physicians of Canada. He married in 1921 Dr. Esther Harrison, who is now a gynaecologist on the staff of the Women's College Hospital, Toronto, by whom he had two sons.

C. M. McINTYRE, M.B., Ch.B.

Dr. C. M. McIntyre, who was in general practice at Bridgend, Isle of Islay, Argyllshire, for a quarter of a century, died recently at the age of 55.

Campbell Melville McIntyre was born at Oban on October 28, 1904, and was educated at Oban High School and at Dollar Academy. He studied medicine at Glasgow University, graduating M.B., Ch.B. in 1927. After graduation he held the appointments of house-surgeon, casualty surgeon, and house-physician at Glasgow Western Infirmary. In 1929 he succeeded his uncle, Dr. Hugh McIntyre, at Bridgend, where he remained in practice until 1954. He was appointed a justice of the peace in 1941, and he was also an honorary sheriff substitute for Argyll.

A. M. C. writes: Many friends will mourn the passing of Campbell McIntyre. It was my privilege to know him well, as a colleague in practice in a neighbouring parish, and I always found him most willing to help when any assistance was required. He was an excellent doctor and was held in the highest regard and esteem by all his patients, to whom he gave unstintingly of his skill and energy. Indeed, though hampered by ill-health for a number of years, he did not spare himself until he was compelled to retire from practice at a comparatively early age. His last few years were marred by considerable suffering, but his burden was made more bearable by the unremitting care and understanding of his wife, to whom and to their son and daughter the sympathy of all friends is extended.

A. J. BEVERIDGE, C.B., O.B.E., M.C., M.Sc. M.B., B.Ch., D.P.H.

The obituary of Major-General A. J. Beveridge was printed in the *Journal* of November 14 (p. 1026).

F. E. H. writes: In addition to his many academic achievements, his Service record, and the decorations conferred on him, "Bev," as of course he was known, had a geniality which may not have been apparent to those who met him only in the course of duty. Once he had walked out of his office with a cheerful, "I'll call it a day now; come to the mess as soon as you can," he was no longer the strict disciplinarian and forceful driver; he became the personal friend of all the other members of the mess. Subsequently I had the privilege of meeting him in his home in Edinburgh while he was A.D.M.S. Scottish Command, and it was clear that he had shown the same personal interest in the officers under his command as in his own family. The death of his wife while he was in Edinburgh was a big blow to him, and resulted in a feeling of loneliness that never left him. Our sympathy is for his sons and daughters in their loss of such a father.

Medical Notes in Parliament

HOSPITAL SERVICE FINANCE AND ADMINISTRATION

The debate on the Hospital Service in the House of Lords on November 19 was mostly concerned with administration. It began with an account of the frustrations of an enthusiastic lay member shackled by lack of resources, but it included also two expert medical contributions on the development of the regional services.

Bureaucracy and Parsimony

Lord STONHAM speaks with experience of the North-west Metropolitan area. He inveighed strongly against the "relentless and blind" opposition of the Treasury and the bureaucracy of the Ministry of Health. To him, the achievements of the ordinary regional hospitals had been won against a disgraceful background of exploitation and parsimony. In real terms, less was being spent on health now than before the war; and he found the answer to his question, "How is it possible to spend less and do so much more work?" in a letter to *The Times* from Dr. McCallum on September 2.

"The answer is shameful. It has been done by cheating. It has been done by relying on the traditions, the goodwill and

devotion, and indeed the 'sweated labour' of those who work in the National Health Service. This country is therefore still enjoying a first-class service on second-class payment. The goodwill that enables it to do so is fast running out."

On capital expenditure he contrasted the B.M.A. view that an average of £75m. a year was needed with the £22m. provided this year, £25½m. next year, and the promised £31m. in 1961–2. Since £15m. of the £31m. was to go to centrally financed major projects and £3m. to the replacement of obsolete equipment, only just over £11m. was left for all the hospital boards in England and Wales —2,500 hospitals, 400,000 staffed beds, nearly 3m. in-patients a year. It was grotesquely inadequate.

Filth and Cross-infection

Only 3.5% of the total spent on the hospital service was spent on maintenance—just 8d. in the £, a cruel and stupid figure. "What does it mean to the condition of actual hospitals? For the five hospitals in my group in smoky, grimy central London it means just one word—filth." The regional boards had not sufficient funds to enable them to maintain the minimum standards of cleanliness that could be enforced in factories. It was not funny, and it became even less so when the gentlemen in Whitehall sent out circulars demanding action about the dangers of cross-infection. The first priority was money to get the hospitals clean. He asked for a fair deal for ancillary and non-medical staffs, a review of salaries, and better negotiating machinery. He also suggested a National Hospitals Board, which should be given an adequate block grant and allowed to get on with the job.

Provincial Hospitals

Viscount WAVERLEY, a consultant physician at the Royal Berkshire Hospital, devoted a maiden speech which attracted much attention to the needs of the non-teaching, mostly provincial, regional board hospitals in meeting an ever-increasing demand. The progressive development of these hospitals, resulting from the steady diffusion of specialist skills, the increasing confidence of family doctors, and the diminishing proportion of patients being transferred to the teaching centres—often coupled with large increases in the population of the area served—had been accompanied by many problems. There was overcrowding in the out-patient clinics, special departments, and wards. The patient-bed turnover had been speeded up so much that there was a risk of breakdown through staff fatigue and inadequate investigation and treatment. Nursing recruitment was jeopardized. There was a serious shortage of physio-therapists, and of technicians in the radiology departments.

The bulk of all clinical material was investigated and treated in the provinces. From there should come a steady and increasing stream of valuable original work. But this was not fostered by conditions of lack of accommodation, crowding, rushing about, and preoccupation with staff shortages. These hospitals deserved much greater support, and the interest of the country required it. The only way out was the immediate launching of a massive programme of new construction. In that respect the Minister's announcement on November 16 was very disappointing. The expanded programme must be accompanied by an imaginative review of conditions of service and rewards in the nursing and ancillary services. The Hospital Service must be able to compete with industry or it would starve. It was not good enough to hope to rely indefinitely on selfless devotion.

"Regional Inferiority"

Lord COHEN OF BIRKENHEAD examined the concept of regionalization put forward in 1948, and found that it had not been realized. It was supposed that the influence of the teaching hospitals, which were put at the functional centre of each of the regions, would permeate throughout the regions. What had happened was that in many, if not most, regions there was no contact between the regional and the teaching hospitals. The old antagonisms had been perpetuated. There was still a feeling of "regional inferiority."

The standards of service in regional hospitals as a whole were not those of teaching hospitals. The difference did not lie in skill, but in staffing, facilities, accommodation, and the like. It was important to carry out clinical and epidemiological studies to elucidate the present situation. Without offering a detailed solution he suggested that the regions were generally too big and sprawling ("After all, one cannot expect the City of Manchester to influence Barrow—and that is indeed what is expected"), and offered Liverpool as an appropriate prototype ("a region in which the teaching hospital is no more than 17 miles from any other hospital in the region, and members of the teaching hospital are on the staffs of almost all the regional hospitals").

He also thought that the isolation of the general practitioner from the hospital was being perpetuated, to the detriment of both, and, after recalling some of the ways which his committee on general practice in 1952 suggested that general practitioners might be integrated in the hospital service, made the point that the development of group practice removed some difficulties.

Parkinson's Law for Hospital Beds

His third point was, "Are we using our hospitals to the best advantage?" If they were pressing the Government to spend more money they must assure the Government that the beds were needed. At the inception of the Service it was suggested that for acute general hospitals five beds per 1,000 population were needed. Recent case-load studies had shown that in many areas that was too high. In Northampton and Norwich the number was nearer two, and in an industrial area investigated under the aegis of the Nuffield Provincial Hospitals Trust it was 2.5. But all the beds were full, wherever they were; there was a Parkinson's law in relation to hospital beds—if you provide them they will be filled, and for much longer periods than they should be filled. The question of numbers must be looked at with much greater care than had been done in the past.

Before Lord TAYLOR came to sum up at the end of the debate, mental and mental-deficiency hospitals had found mention by Lord PAKENHAM and others, with an eye to a future discussion, the BISHOP OF CHICHESTER had entered a special plea for spiritual healing and the place of the hospital chapel, Lord AUCKLAND had brought in the needs of the maternity service, and Lord CHORLEY had claimed the right of patients who so wished to be by themselves ("the general ward of a great hospital is not a place where it is possible to obtain seclusion") by the provision of small or private wards in greater numbers.

Cost and Administration

Lord TAYLOR tackled first the financial provision for the Service. The total cost for the Hospital Service was about £400m. a year, 57% of the cost of the Health Service. A recent report from the International Labour Office had shown that the cost of medical care in most developed countries was between 3.7% and 4.5% of the national income. Britain's proportion was 4%. To equal the 4.4% of Canada and France would mean an extra £67m. a year. Were we prosperous enough to spend that amount? He thought we were, and that the additional amount would enable all that they had in mind to be done. For 10 years hospitals had been starved of capital and maintenance expenditure. The B.M.A. figure of £75m. a year as the proper capital expenditure had been mentioned; but they would be well content if the figure reached £50m. in a reasonable time.

He hoped for a great deal on the design and construction side from the advances made in architecture, the establishment of the Advanced Architecture Division of the Nuffield Provincial Hospitals Trust, and the appointment of Mr. Tatton-Brown as chief architect at the Ministry of Health.

But there must also be simpler control of cost, by a block allocation of money, and the elimination of interminable delays and reference-back methods by a clear allocation of responsibility and power to act. There must also be a proper percentage earmarked for maintenance, a problem for the advisory council on management and efficiency set up under Sir Ewart Smith.

Delays in day-to-day management arose from the five-tier system. The awful complication of detailed Parliamentary accountability he condemned as rule by circular and policy-making by the making of returns—an absolute farce. A further difficulty was the multiplicity and size of committees. The answer was to reduce management committees and regional boards to eight members, and forbid the formation of subcommittees. The representative functions they were supposed to perform needed something quite different, in his view large advisory councils meeting in plenary session once or twice a year for a "grand inquest" on the work of the committee or board. The regional hospital boards were bodies corporate, and should be allowed to behave as such, free from Treasury or Ministry control except in regard to their overall budgetary allocations and national negotiated agreements.

Government Reply

The Government reply was delivered by Lord ST. OSWALD, a Lord in Waiting. He questioned whether the Labour Party, if in power, would regard the B.M.A.'s findings and advice (£75m. a year for hospital building) as binding on their Minister of Health. Returning to this point in a later passage, Lord St. Oswald said it was reasonable to hope that the current upward trend could be maintained, and that the £50m. a year mentioned by Lord Taylor would be reached.

Lord St. Oswald claimed that there was a dramatic expansion in progress in the Hospital Service, and an ambitious programme that included over 150 major projects in course of construction or planning. Six new hospitals were already in extensive use, although further building remained to be completed. It seemed hardly relevant to the arguments that had been advanced to add, as he did, that "if, as projects, they had in the first place been less ambitious, they could be referred to now as new completed hospitals," even as a preface to the recital of the new work announced during the previous fortnight. There was more realism in a later observation that "it is true that a number of these 30 hospitals have not advanced very far beyond the proverbial twinkle in the Minister's eye."

The Ministry's design unit was at work on a series of studies; it was being greatly expanded, and would design certain hospital departments to be built in different areas. One aim would be to demonstrate the cost, and the lessons learned from detailed costing would be passed on to hospital authorities. The Ministry would take increased initiative in getting more information to hospital boards about design in the earlier stages of planning, and thus save time later.

He promised study of the idea for central control of the service under a National Hospital Board or corporation, but saw little possibility of surmounting the stern difficulty of entrusting the spending of hundreds of millions raised by taxation to a body outside the control of Parliament. Similar proposals to those advocated by Lord Taylor had been rejected by the Guillebaud Committee on the grounds that the gain in administrative efficiency was dubious and the loss of representation of the community would be too high a price to pay. He pointed out that the gross cost of the Health Service as a percentage of the gross national product had dropped yearly from 3.84 in 1949–50 to 3.24 in 1954–5; since then it had been rising steadily, and from 1958–9 was estimated at 3.49.

SUPPLEMENTARY PROFESSIONS BILL

The Professions Supplementary to Medicine Bill was presented in the House of Commons on November 18, and given a first reading. It provides for the statutory registration of members of the following professions in England, Wales, Scotland, and Northern Ireland—chiropodists, dietitians, medical laboratory technicians, occupational therapists, physiotherapists, radiographers, remedial gymnasts, and speech therapists—and includes machinery for regulating their professional education and conduct.

Council and Boards

There is to be a Council for Professions Supplementary to Medicine, and a registration board for each profession. Each board will keep a register of persons qualified to practise, and will also have the general task of promoting standards of professional education and conduct. On each board the representatives of the profession concerned will have a majority of one, and the remaining members will include medical practitioners and experts in professional education. The Council, which will be responsible for the general co-ordination and supervision of the work of the boards, will have 23 members—eight members of the registered professions; eight medical practitioners; and seven independent members of whom four (including the chairman) will be nominated by the Privy Council, two by the Health Ministers in England and Scotland, and one by the Governor of Northern Ireland.

Training courses and qualifications will be subject to the approval of the boards, the Council, and the Privy Council. The syllabus of training is to be submitted for approval to the boards by the professional organizations concerned, and the syllabus as approved will be taught in approved hospital schools, private schools, technical colleges, etc. A person who has obtained an approved qualification will be entitled to registration, and only those on the register may use the relevant title—e.g., "State-registered chiropodist." For improper use of the title there are penalties including a maximum fine of £50 on summary conviction, and of £100 on second or subsequent conviction. Each profession will have a disciplinary committee, and among the grounds on which a committee can direct that a person's name shall be removed from the register will be "infamous conduct in any professional respect." There is a right of appeal to the Judicial Committee of the Privy Council.

Medico-Legal

THE DEFENCE OF "USUAL PRACTICE" IN NEGLIGENCE CASES

[FROM OUR LEGAL CORRESPONDENT]

On November 18 the Court of Appeal delivered reserved judgments (Lord Justice Morris dissenting) allowing an appeal by Dr. Jack Stephen Rix, a general practitioner, of Brentwood, Essex, against a judgment of Mr. Justice Barry finding him guilty of negligence. Agreed damages of £9,050 had been awarded. The plaintiff's cross-appeal was dismissed (*The Times*, November 19).

Accident to Butcher

In 1955 Mr. Chapman, a butcher, was boning a rump of beef when his knife slipped and wounded his abdomen. Dr. Rix happened to be at Brentwood District Hospital (a cottage hospital with no resident medical staff) when a telephone call was received there concerning the accident. Dr. Rix examined Mr. Chapman at the butcher's shop and saw a wound 1½ in. (3.7 cm.) long which was not bleeding profusely. He examined him again at the hospital, and concluded that, though the deep fascia had been cut, the wound had not penetrated the peritoneum. Dr. Rix ordered the wound to be stitched and dressed, and sent Mr. Chapman home with strict instructions to see his own doctor that evening. Mr. Chapman told his own doctor, Dr. Mohr,

that he had been told at hospital that the wound was "superficial": Dr. Rix did not communicate with Dr. Mohr direct. Dr. Mohr did not appreciate that the hospital was a cottage hospital and that Dr. Rix was not a casualty officer, and so he was not made aware that it was for him to decide whether or not the wound was superficial.

Two days after Mr. Chapman was sent home, he was admitted to hospital with acute peritonitis and died after an operation. It was common ground that had there been surgical treatment on the day of the accident Mr. Chapman would have lived. A post-mortem examination revealed that the wound had penetrated the small intestine.

Failure of Communication

Mr. Justice Barry at first instance dismissed all the charges of negligence against Dr. Rix except one. Mr. Justice Barry, upheld by all the judges of the Court of Appeal, held that Dr. Rix had not been negligent in his diagnosis, although it was too optimistic. The only finding of negligence against Dr. Rix at first instance was that he had been negligent as a doctor in failing to communicate directly by telephone or letter with Mr. Chapman's own doctor after dealing with Mr. Chapman in an emergency. Lord Justice Morris, in his dissenting judgment, agreed with this finding. Lord Justice Morris referred to Dr. Rix's evidence that it was not the practice in his area for one doctor to write to another doctor when sending the latter's patient to him, and that he could not have told Dr. Mohr anything which Mr. Chapman could not have told him or which Dr. Mohr could not infer from Dr. Rix's actions. However, Dr. Mohr had been misled, although he was in no way criticized. Lord Justice Morris did not accept the evidence that Dr. Rix could not have usefully told Dr. Mohr anything, and in his view this was in any event a special case where no standard medical practice could be said to exist.

Law on "Usual Practice"

The classic statement of the law in such cases as this was stated by Lord Clyde[1] in a passage adopted by Lord Justice Romer (one of the two judges forming the majority in this appeal):

> "To establish liability by a doctor where a deviation from normal practice is alleged, three facts require to be established. First of all it must be proved that there is a usual and normal practice. Secondly it must be proved that the defender has not adopted that practice, and thirdly (and this is of crucial importance) it must be established that the course the doctor adopted is one which no professional man of ordinary skill would have taken if he had been acting with ordinary care."

Lord Justice Romer and Lord Justice Willmer, forming the majority of the Court, held that these three conditions were not satisfied. In the light of what was now known of the case it would have been better if Dr. Rix had written to Dr. Mohr, but the case must be decided in the light of the situation at the time, and on the evidence such communication was not the kind of precaution which in practice was regularly adopted between general practitioners. For that reason the finding of negligence against Dr. Rix could not be supported. Leave was granted to appeal to the House of Lords.

As Lord Clyde indicated in the passage quoted, conformity with the usual practice may well be negligence in some cases, either because medical science has advanced or because the case is exceptional and out of the general run of things. In either case, the practitioner following the usual practice is negligent only if he ought to have known of the advance of medical science, or if he ought to have been aware of the exceptional nature of the circumstances. Dr. Rix treated this case as a normal transaction between one general practitioner and another. In fact, Dr. Mohr was misled into thinking that this was not a transaction of that type, but that the message given to him came with all the authority of a clinical examination in a fully staffed and fully equipped hospital.

[1] *Hunter* v. *Hanley* [1955] *Scots Law Times* 213.

Warning for the Future

Dr. Rix was acquitted of negligence because there was no reason why he ought to have been aware of the exceptional nature of the circumstances. However, if a similar case were to recur now, the courts might hold that practitioners ought to have benefited from Dr. Rix's experiences and should possess a more astute awareness of possible consequences.

SPEEDING ON EMERGENCY CALLS

[FROM OUR LEGAL CORRESPONDENT]

On November 4 Dr. John McLaughlin, a general practitioner in Accrington, was fined £4 and his licence was endorsed by the Accrington magistrates for speeding at 48 miles an hour in a built-up area, despite his plea that he was on his way to an emergency case (*Manchester Guardian*, November 5).

The magistrates stated that they accepted Dr. McLaughlin's case that, on his return to surgery from an urgent call on the evening of October 7, he had found two other urgent calls, one to a case of suspected thrombosis and the other to a case of haemorrhage, and that when stopped by the police he was on his way to the haemorrhage case. The magistrates felt, however, that it would be wrong to put doctors above the law, and they refused to accept the suggestion of Dr. McLaughlin's solicitor that this was a case where an absolute discharge would be appropriate.

"Special Reason" as a Defence

The magistrates also refused to find that the circumstances of the case constituted a "special reason" within the meaning of section 5(1) of the Road Traffic Act, 1934: the effect of that section is to make endorsement of the driver's licence mandatory on a conviction for speeding "unless for any special reason the court thinks fit to order otherwise." In a strong *dictum* in a case on appeal in 1946,[1] Lord Goddard said that the "special reasons" must be special to the offence and not to the offender. He gave as two of several examples of reasons special to the offence, "a driver exceeding the speed limit because he has suddenly been called to attend a dying relative or a doctor going to an urgent call." Lord Goddard also gave as an example of a reason special to the offender, and therefore not in ordinary circumstances a "special reason" within the meaning of the Act, the mere fact that the driver was a doctor. It is not the driver's profession or personal circumstances which may be looked at as a "special reason," but the objective of the deed concerned in the charge. Lord Goddard's statement of the law in this case was, in so far as it dealt with speeding offences, *obiter*, and therefore not binding on the courts to-day, though no doubt his words are persuasive.

In this connexion the terms of section 3 of the Road Traffic Act, 1934, are of interest:

> "The provisions of any enactment . . . imposing a speed limit on motor vehicles shall not apply to any vehicle on an occasion when it is being used for fire brigade, ambulance, or police purposes, if the observance of those provisions would be likely to hinder the use of the vehicle for the purpose for which it is being used on that occasion."

However, in a Scottish case in 1937,[2] it was held that a person driving his private car in order to obtain evidence of infringement of the law by a police car is not using his car for police purposes. If the English courts were to follow the analogy of this case it is at least doubtful whether a doctor would be held to be using his car for ambulance purposes even when he was taking a patient to hospital in it. However, the English courts are not bound so to extend this authority by analogy, nor in view of the narrow grounds of the decision are the Scottish courts bound to do so.

[1] *Whittal* v. *Kirby* [1946] 2 A.E.R. 552.
[2] *Strathern* v. *Gladstone* [1937] S.C. (J) 11.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **November 7** (No. 44) and corresponding week 1958.

Figures of *cases* are for the countries shown and **London administrative** county. Figures of *deaths* and *births* are for the **whole of Engla d and** Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	3	0	5	0		6	3	5	0	3
Dysentery	443	45	193	3	1	551	46	154	3	9
Encephalitis, acute	2	1		0		2	0		0	
Enteric fever:										
Typhoid	3	1	0	0		4	1	1	1	
Paratyphoid	9	0	0	0	1(B)	5	0	2(B)	0	
Food-poisoning	177	36	16	0		205	15	9	0	
Infective enteritis or diarrhoea under 2 years				19	31				5	38
Measles*	1,196	22	15	0	42	5,014	300	60	25	210
Meningococcal infection	14	2	6	1	3	17	1	6	2	
Ophthalmia neonatorum	18	3	6	0		15	2	5	0	
Pneumonia†	177	13	111	6		316	23	144	1	
Poliomyelitis, acute:										
Paralytic	12	2	0	0		54	4	19	1	8
Non-paralytic	2	0	0			25	1			
Puerperal fever§	199	24	13	2		237	34	11	0	
Scarlet fever	1,025	48	147	22	36	889	66	128	19	41
Tuberculosis:										
Respiratory	430	41	54	14		502	51	104	21	
Non-respiratory	50	7	13	2		56	8	18	1	
Whooping-cough	568	26	130	5	89	637	21	64	54	69

DEATHS	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire
Diphtheria	0	0	0	0	0	1	1	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	7	0	0	0	1	6	0	0	0	1
Influenza	22	1	0	1	1	8	1	1	0	1
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		1	0				0	0		
Pneumonia		34	19	11	7	393	27	16	1	3
Poliomyelitis, acute	1	0		0	0	4	1		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	63	3	5	2	3	67	5	10	0	1
Non-respiratory		0	0	0	0		1	0	0	1
Whooping-cough	0	0	1	0	0	2	0	0	1	0
Deaths 0–1 year	314	33	28	8	17	281	28	21	6	20
Deaths (excluding stillbirths)	9,208	779	540	133	154	8,982	722	496	107	134
LIVE BIRTHS	13,385	1063	897	260	340	13,484	1199	934	200	361
STILLBIRTHS	248	22	22			296	42	17		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

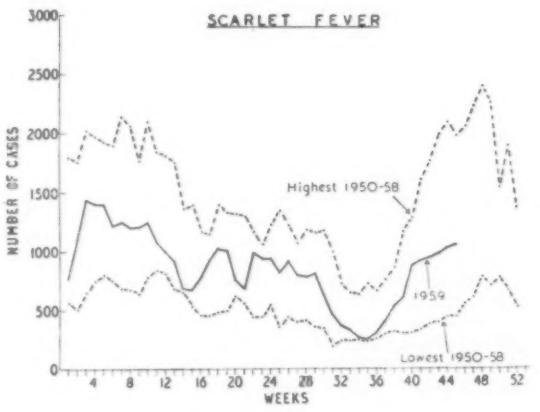
Infectious Diseases

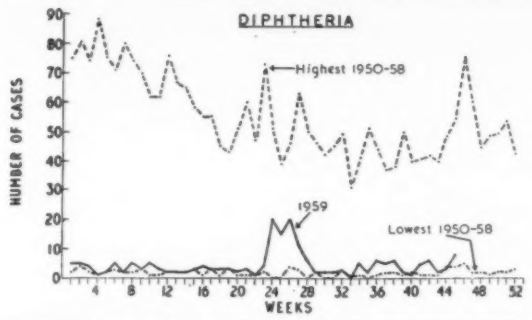
Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Nov. 7	Week Ending Nov. 14
Acute Poliomyelitis		
London	2	7
Islington	0	2
Lancashire	1	4
Dysentery		
Lancashire	123	147
Bolton C.B.	5	10
Worsley U.D.	17	37
London	45	59
Southwark	6	12
Surrey	15	22
Warwickshire	32	22
Coventry C.B.	27	14
Yorkshire East Riding	8	17
Haltemprice U.D.	2	14
Yorkshire West Riding	96	106
Barnsley C.B.	21	20
Bradford C.B.	2	17
Leeds C.B.	19	23
Glamorganshire	3	22
Cardiff C.B.	6	17
Glasgow	104	162
Dundee	19	30
Typhoid Fever		
London	1	5
Islington	0	4
Diphtheria		
London	0	7
Islington	0	6

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





Universities and Colleges

UNIVERSITY OF OXFORD

Additional Goodger scholarships for 1959–60 have been awarded to Dr. O. A. A. Bock (University College) and Mrs. Katherine I. Simnett (Somerville College).

The Martin Wronker prize in medicine for 1959 has been awarded to David Keith Parkinson (Christ Church).

UNIVERSITY OF CAMBRIDGE

Dr. R. T. Sims has been reappointed a University Demonstrator in the Department of Anatomy, with tenure from April 1, 1960 for two years.

In Congregation on October 31 the following degrees were conferred:

M.D.—H. G. Ll. Lloyd-Thomas.
M.B., B.CHIR.—*G. Herbert.
M.B.—*J. S. Grimshaw, P. V. Hunt.
*By proxy.

UNIVERSITY OF EDINBURGH

The following appointments are announced: Drs. M. G. Kerr, E. M. Chinnan, D. M. Mackinnon, Heather S. Fulton, and G. Meikle, Demonstrators in Anatomy; Dr. K. Kuczynski, Senior Lecturer in Anatomy; Mr. T. J. McNair, Lecturer in Clinical Surgery; Dr. Constance Gibbs, Lecturer in General Practice Teaching Unit; Dr. S. H. Taylor, Lecturer in Medicine; Dr. P. C. Robertson, Assistant Lecturer in Medicine; Mr. J. H. S. Scott, Senior Lecturer in Orthopaedic Surgery; Dr. A. A. Shivas, Senior Lecturer in Pathology; Dr. G. D. Forwell, temporary Lecturer in Public Health and Social Medicine; and Mr. Bernard Nolan, Lecturer in Surgical Science.

Dr. I. D. Heath resigned from the appointment of Assistant in the Department of Anatomy, and Dr. J. A. D. Anderson from that of Lecturer in the General Practice Teaching Unit on September 30, 1959.

UNIVERSITY OF LONDON

Mr. W. J. Dempster, Lecturer in Experimental Surgery at the Postgraduate Medical School of London, has been appointed to the Readership in Experimental Surgery tenable at that School.

The title of Reader in Biochemistry in the University of London has been conferred on Dr. S. P. Datta in respect of his post at University College.

UNIVERSITY OF BIRMINGHAM

Sir Arthur Thomson has been reappointed representative of the University on the General Medical Council from October 1, 1959, to September 30, 1961.

Professor T. McKeown has been appointed representative of the University on the Birmingham Regional Cancer (Co-ordinating) Committee.

The following appointments are announced: Dr. G. Cumming to be Lecturer in Medicine from October 1, 1959; Dr. L. A. G. Davidson, University Research Fellow, to be Lecturer in Medicine from July 1, 1959; Dr. C. G. Caro to be temporary Lecturer in Medicine from October 1, 1959, to September 30, 1960; Dr. G. H. A. Hübscher, University Research Fellow, to be Lecturer in Medical Biochemistry and Pharmacology from October 1, 1959; Dr. I. M. Leck, Research Fellow, to be Lecturer in Social Medicine from October 1, 1959; and Dr. C. E. Oxnard to be Research Fellow in Anatomy from August 1, 1959.

Sir Arthur Thomson, Professor of Therapeutics since 1947, Dean of the Faculty of Medicine since 1951, and Vice-Principal of the University from 1952 to 1957, retired on September 30, 1959.

The following resignations are announced: Dr. B. Shaw, Lecturer in Medical Biochemistry and Pharmacology, on September 30, 1959; Dr. G. H. Armitage, Lecturer in Medicine, on June 30, 1959; and Mr. G. H. Baines, part-time Lecturer in Surgery, on September 30, 1959.

ROYAL COLLEGE OF PHYSICIANS OF LONDON

At a quarterly comitia of the College, held on October 29 with the President, Sir Robert Platt, in the chair, the award of the Jenks Memorial Scholarship to G. A. C. Welply, late of Epsom College, was announced.

Licences

Licences to practise were conferred upon the following 133 candidates who had passed the final examination in medicine, surgery, and midwifery of the Conioint Board and who had complied with the by-laws of the College:

G. O. Alabi, R. M. J. Andrews, C. L. C. Arnold, N. A. Atalla, D. Atkins, H. Baderman, R. B. Barrett, J. G. Bass, J. F. Bedell, V. B. Bhardwaj, J. Brittain, Shelagh M. Broadway, D. M. Broughton, D. Bunnag, P. E. Burke, A. B. Byles, J. M. Campbell, Rosemary J. Chambers, Marion R. Chaplin, A. F. S. Childs, C. E. P. Clarke, A. B. Clymo, J. C. Collings, G. I. Collins, L. P. Connolly, I. B. Copley, Patricia L. Crawford, S. Crown, J. S. Cumming, R. A. C. Davies, D. Denis-Smith, K. A. Doe, J. M. A. Dyer, F. W. L.-T. Engmann, Diana A. M. Ernaelsteen, P. F. C. Eyre, G. C. Fox, J. Fraser, R. W. Gabriel, M. J. Gallant, F. R. Gamman, N. F. C. Gane, J. R. Garrett, D. Godwin, R. P. Golding, J. Gough, W. A. Gould, W. E. Greaves, Kathleen Green, R. F. Gunstone, Lydia M. Hayes, B. Higgs, Ann J. Hill, K. Hollinrake, M. J. H. Homewood, D. F. Hopkins, F. T. Horan, M. J. K. Hudson, M. F. Hyatt, E. O. Iwenofu, F. H. A. Jago, S. M. N. Jaikaran, Jai Kumari, R. W. John, Josephine I. Johnston, Gillian A. Jonas, E. V. Jones, I. W. Jones, Marion E. Knighton, Eva M. Kohner, D. Lamb, D. N. Landon, J. W. Latham, P. W. Lord, J. J. MacMahon, Helen M. McG. McNie, K. S. A. Madgwick, D. M. Marsh, R. D. Marshall, Ann S. Mason, J. S. Mather, L. W. Morrish, D. N. E. Myers, M. J. Noronha, J. O. Oluwasanmi, R. B. F. Orr, W. J. C. Parker, C. B. Patel, J. C. D. Plant, G. M. Preston, M. Rendall, D. A. Richards, E. H. Richards, J. R. Ll. Roberts, J. S. Robinson, I. C. Roddick, Ann T. Roden, Ann Simpson, J. McL. Singleton, Jane Skinner, E. K. M. Smith, M. E. Smith, I. T. Stuttaford, E. J. L. Taylor, C. H. C. Thomas, A. J. Thompson, P. G. R. Tingley, D. J. Tooby, Catherine R. Townsend, J. Townsend, R. R. Trayner, Ann Whitfield, Jennifer A. Whitlock, S. P. Wickremasinghe, D. C. Wilson, M. St. G. Wilson, M. B. Wilson, M. C. Winterton, C. C. Wise, C. Wynne.

Diplomas

Diplomas in Child Health, in Ophthalmology, in Physical Medicine, and in Tropical Medicine and Hygiene were granted, jointly with the Royal College of Surgeons of England, to the following successful candidates:

DIPLOMA IN CHILD HEALTH.—Audrey B. Abrams, S. N. Anandaraja, Zeenat Ansari, L. B. Bartlet, Aileen E. F. Benson, K. M. Bhat, D. P. Birkett, Margaret I. Blackhall, Joyce O. M. Board, R. V. Boyd, Marita R. Brown, S. A. Bryans, L. M. Burke, R. P. Carrington, J. V. F. Catto, F. L. W. Collings, G. F. N. Collins, G. F. Counsell, Colleen A. Cox, J. H. Darrell, S. H. Dave, Helen A. Davidson, J. G. Davies, Joy Davies, Margaret S. Davies, I. E. Doney, Patricia A. Doran, Sheila M. Eades, P. C. Elwood, J. J. Enright, D. I. K. Evans, Joyce M. Eyre, A. M. M. Faris, Valerie Farr, B. N. D. Fernando, P. I. Frank, G. Gaire, H. R. Gamsu, G. S. Graham, N. P. S. Gunaratna, J. P. Hawe, Jennifer Hill, Irene Holbrook, Margaret Hollands, I. B. Houston, Ann L. Hunter, Elizabeth J. Ives, Jacqueline A. Jackson, A. E. F. Jayesinghe, K. I. John, J. K. Johnson, M. S. Jolly, Barbara D. Jones, J. H. Keen, G. W. Knox, L. S. Kotagama, S. K. Kothari, M. Krishnaswamy, Shirley A. Leslie, Sheila R. Lewis, Connie K. L. Lim, Gillian B. McCullagh, J. A. W. McKelvey, F. C. McNeila, Ma Mya Kyi, Elsie D. May, H. P. Mehra, D. H. Melville-Swarries, Margaret A. Mills, I. Mohammed, D. Mohan, B. K. Mukherji, P. A. Murphy, Nora M. Norris, A. Nozari, Y. H. Nuwayhid, Brenda B. O'Donnell, Gweneth L. O'Reilly, B. J. O'Sullivan, Jean B. Owens, R. Prosser, K. T. Rackham, S. S. Rajan, B. A. Rapier, Riyazuddin, Sheila M. Russell, S. J. Shah, Satayavati Sharma, M. Silver, A. P. Singh, R. P. Sinha, G. H. Smerdon, R. V. Somaia, Catherine I. Soutter, T. I. Stewart, S. G. Sutton, Ursula Tarpey, O. Thananskul, C. Thavarasook, Norma C. M. Theobalds, W. Turner, H. R. Vadanagara, J. A. M. Vasey, J. V. Violet, Elizabeth Wales, Hazel M. Wilson, C. B. S. Wood, H. G. Wotherspoon, G. B. Wyatt, Yu-Leung Yeung.

DIPLOMA IN OPHTHALMOLOGY.—Aung Than, T. L. F. Averill, K. L. Batten, M. J. A. Britten, W. H. Clarke, Anthea M. S. Connell, M. S. Dawood, A. Freedman, R. N. Ghosh, M. El S. Ibrahim, E. O. Jacobs, B. S. Jay, S. M. Kamaluddin, T. D. Leckie, R. D. Loudon, D. J. McAuliffe, J. von L. Malan, Khalida Naib, R. S. Naniundaswamy, Jean A. Peachey, J. F. Pereira, R. J. Pyne, N. S. C. Rice, I. F. Robertson, P. V. Rycroft, M. O. Sheriff, S. M. Siddique, I. Singh, D. Staig, W. E. Staples, J. M. Straiton, F. P. Sullivan, R. P. Tandon, J. N. Taylor, Tha Khin, P. Wright.

DIPLOMA IN PHYSICAL MEDICINE.—J. R. Burrows, L. Koadlow, L. H. Truelove, P. K. B. White.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—S. H. Ali, D. P. Arya, J. Barnes, Hildegard Birkhahn, R. J. P. Blyth, E. G. Budiyappa, D. M. Devane, A. H. Dossal, M. Ehtishamuddin, P. Faridian Aragh, S. M. Faruque, M. D. Goulding, M. A. Halim, A. G. Harwood, M. F. Hasan, D. S. Hutton, P. N. Jha, J. S. Karcher, H. A. Khan, M. A. Khan, E. P. Lawrence, Wan-Yee Lo, F. R. Manuel, M. M. Mehta, G. G. Meilland, F. W. Murphy, K. G. Patel, L. C. Patel, S. P. Rastogi, M. Raza, Hilary M. Rowson, I. B. Sardharwalla, G. S. Sethi, N. Z. Shaikh, A. S. Shera, A. B. Shrestha, J. A. Siddiqui, W. G. Strauss, C. R. Tribe, D. M. Wayte, H. W. Whittingham, D. N. Wysham, Lois R. Zimmerman.

Medical News

Association of Anaesthetists' Prize

The Council of the Association of Anaesthetists of Great Britain and Ireland is offering a prize of 200 guineas for the best essay based upon new and original work related to the subject of general anaesthesia for dental surgery. Details may be obtained from the Honorary Secretary of the Association, 47, Lincoln's Inn Fields, London, W.C.2. The closing date is March 1, 1961. (See *Journal*, advertisement page 69.)

New Virus Laboratory at Queen's University, Belfast

The National Fund for Poliomyelitis Research is to make a grant of £70,000 to build a new virus laboratory at Queen's University, Belfast. The grant has been offered on condition that the university and the Northern Ireland Hospitals Authority also contribute to the building, although it is understood that this may not be possible until a later date. It is hoped that building will start shortly.

College of General Practitioners

Professor A. M. CLAYE, P.R.C.O.G., as President of the youngest College but one, gave his blessing to the C.G.P. at its dinner last week.

General practitioners, he said, retained the personal touch with patients which some seemed these days to be in danger of losing in consulting practice. As an instance of the desire of his College to have a closer relationship with the College of General Practitioners, Dr. M. I. COOKSON, of Gloucester, would be attending its next council meeting. Replying to the toast, Dr. IAN GRANT, retiring President of the C.G.P., expressed once again their indebtedness to the Society of Apothecaries for lending them its lovely Hall as a meeting-place. Dr. Grant said they had looked into the question of an entrance examination and were recommending that those graduating from 1960 onwards would have to take one. They were unable to go ahead with their scheme for a home in Lincoln's Inn Fields, but under Sir HARRY JEPHCOTT they hoped to launch soon an appeal for funds. The health of the guests was proposed by Dr. G. I. WATSON, who said: "The wine in our glasses is warm with gratitude to all our guests and friends wherever they are." In reply, Dr. R. R. TRAIL paid special tribute to Dr. JOHN HUNT, the honorary secretary, for the enthusiasm and energy he put into the work of the College, which now had more than 5,000 members in this country and in the Commonwealth.

Medical Photography

The recent annual exhibition of the Medical Group of the Royal Photographic Society was a remarkable demonstration of the fine work now being done in the photographic departments of British hospitals. Before the exhibition was opened the following trophies, etc., were presented:

(1) By the Association of British Pharmaceutical Industries, to Mr. A. L. WOODING for the best series of colour prints; (2) by the Pharmaceutical Society, the Beginner's Trophy to Mr. R. MORTON for the best print or prints submitted by a medical photographer of not more than two years' appointment; (3) the Chairman's Trophy to Mr. R. MCVITIE WESTON "for his early work which culminated in the formation of the Medical Group, and which in these more sophisticated days we are apt to forget." And the following certificates were awarded: (1) for the best coloured transparencies, to the Department of Medical Illustration, Manchester Royal Infirmary; (2) for the best print quality, to Mr. E. VICTOR WILLMOTT; (3) for the best teaching series, to Miss SUSAN FRY.

Central Midwives Board

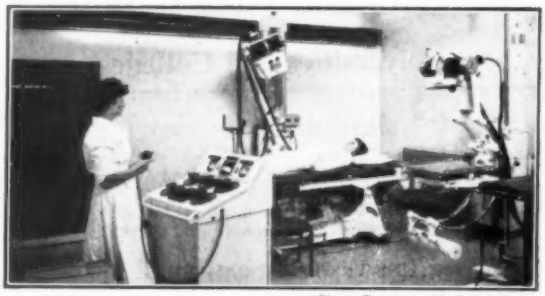
The Board's annual report for the year ended March 31, 1959, announces that during this period Professor A. M. CLAYE, Miss E. J. MERRY, and Mr. V. LACK retired from the Board, their places being taken by Mr. A. C. H. BELL, Miss M. E. HOLLINGWORTH, and Professor W. C. W. NIXON respectively. Mr. A. WALKER and Professor A. A. MONCRIEFF were re-elected as chairman and deputy chairman.

During the year the birth rate rose and the strain on the maternity service predicted by the Board became apparent. Of the 67,768 midwives whose names were on the Midwives Roll on March 31—an increase of 3,046 on the year before—only 16,445 notified their intention to practise.

Sheffield City General Hospital

The new *x*-ray department at Sheffield City General Hospital was opened recently by the EARL OF SCARBOROUGH.

It replaces a department first brought into use in 1915, and incorporates all the recommendations recently published by the Ministry of Health for protection against radiological hazards. The department cost £100,000 and contains eight *x*-ray rooms,



[Photo Finishers (Sheffield), Ltd.

including the one equipped for tomography and skull work shown here, as well as dark-rooms, radiographers' rooms, a visiting-room, and the necessary offices. With the new physiotherapy department which was opened last year, the department forms the first stage of a radical rebuilding scheme for the hospital.

"Chemist and Druggist" Centenary

A cocktail party to mark 100 years of publication was given in honour of the *Chemist and Druggist* at Apothecaries' Hall on November 17 by the publishers, Morgan Brothers, Ltd.

The editor of the *Chemist and Druggist*, Mr. O. H. WALLER, presented a silver salver to the president of the Pharmaceutical Society of Great Britain, Mr. G. HUGHES, with the dry comment that, though his journal had to chastise the Society from time to time, the gift was "in no way a conscience salver." The salver, made in London in 1790 by EDWARD JAY, will be added to the collection of ceremonial silverware which the Pharmaceutical Society has recently been accumulating.

"International Journal of Air Pollution"

This new quarterly journal is edited by Dr. R. S. SCORER (department of mathematics, Imperial College, London, S.W.7), Mr. G. NONHEBEL (I.C.I. House, Millbank, London, S.W.1), Dr. J. PEMBERTON (department of social and preventive medicine, Clinical Sciences Building, Grosvenor Road, Belfast, N. Ireland), and Professor A. J. HAAGEN-SMIT (California Institute of Technology, Pasadena, California, U.S.A.), and it has an international advisory board. Details of subscription rates for organizations and for individuals from the publishers, Pergamon Press Ltd., 4–5, Fitzroy Square, London, W.1.

"Revue de Médecine Psychosomatique"

This new French journal will be published four times a year, and in addition to clinical articles it will include the proceedings of the Société de Médecine Psychosomatique, and a bibliography and critical analysis of relevant published work. The editors are Dr. L. CHERTOK and Dr. M. SAPIR, and British members of the international editorial board are Dr. M. BALINT and Dr. R. MAC KEITH. A year's subscription is 2,300 fr., and inquiries should be sent to the publishers, Les Editions de Médecine Pratique, 12, Rue Pierre-Geofroix, Colombes (Seine), Paris.

International Society for Tropical Dermatology

The Society was founded during the International Congress for Tropical Medicine and Malaria, held in Lisbon in 1958, and the members of its organizing committee are Professor

A. CASTELLANI, Dr. G. C. ANDREWS, Dr. A. C. CIPOLLARO, and Dr. F. REISS, from whom details may be obtained at 870, Fifth Avenue, New York, 21, U.S.A.

Academy of Medicine, Singapore

The following office-bearers and honorary members have been elected for the ensuing year:

Master: Dr. C. E. FIELD; *Assistant Master:* Dr. G. HARIDAS; *Scribe:* Dr. G. AH LENG; *Bursar:* Dr. N. C. SEN GUPTA; *Bedell:* Mr. D. W. C. GAWNE; *Censors:* Professor G. A. RANSOME, Dr. LIM KEE LOO, Dr. J. W. HOE, Dr. G. KEYS SMITH, and Mr. Y. COHEN; *Honorary Members:* Dr. R. A. HICKLING, Sir STANLEY DAVIDSON, and Professor JOHN BRUCE.

"British Medical Students' Journal"

A rugger player with a skull tucked underneath one arm decorates the cover of the Autumn *B.M.S.J.*, and the contents are an equally enticing blend of the solid, the humorous, and the macabre. Useful hints on how to misuse the English language, exasperate the examiner with medical jargon, and conceal ignorance with "etc." are given in "Exam-manship for Grimsdykes." (Price 6d. from British Medical Students' Association, B.M.A. House, Tavistock Square, London, W.C.1.)

Opposition Front Bench, 1959–60

The Rt. Hon. Dr. E. SUMMERSKILL and Mr. K. ROBINSON have been appointed to speak on the Front Bench for the Opposition on health.

Dr. Wilfred Harris Aged 90

The many friends and admirers of Dr. WILFRED HARRIS, whose reputation as a neurologist is international, will be interested to hear that he celebrates the 90th anniversary of his birth on December 2.

Necropsy after Nine Centuries

A two-year examination of the body of Pope CLEMENT II, who died in 1047, has established that he died from lead poisoning, though it has not been possible to say how the poisoning came about. (*The Times*, November 23).

Aberdeen University

The following appointments have been made:

Dr. R. D. CAMPBELL (terminable lectureship, anatomy); Dr. G. INNES and Mr. G. A. SHARP (senior research fellowships, mental health); Dr. R. K. DUTTA (junior research fellowship, physiology).

COMING EVENTS

Pharmaceutical Society of Great Britain.—Dr. H. JACKSON (Head of Department of Experimental Chemotherapy, Christie Hospital, Manchester): "Antifertility Substances," December 3, 7.30 p.m., at the Society's House, 17, Bloomsbury Square, W.C.1.

Heberden Society.—Annual General Meeting, December 4 and 5, Wellcome Foundation, Euston Road, London, N.W.1. Details of programme from the secretary of the Society, c/o Empire Rheumatism Council, Faraday House, 8–10, Charing Cross Road, London, W.C.2.

Seminar on Mental Health.—Sunday seminar for Sussex medical practitioners, Royal Pavilion, Brighton, December 6, Details from Dr. W. S. PARKER, Royal York Buildings, Brighton, 1 (Tel. 29801).

Harben Lectures, 1959: Royal Institute of Public Health and Hygiene.—Sir FRANCIS WALSHE, F.R.S.: "The Evolution of Ideas in Neurology during the Past Century, and the Future of Neurological Medicine." At the Institute's Lecture Hall, 28, Portland Place, W.1, December 8, 9, and 10, at 5 p.m.

British Institute of Radiology.—Annual congress and exhibition, December 10 and 11, Church House, Westminster. Details from the Institute, 32, Welbeck Street, London, W.1.

University College, London.—Evening reception and reunion at the College, February 19, 1960, 6.30 to 9 p.m. Undergraduates or postgraduates entering 1946–50 invited. Applications for tickets, before December 31, to the Assistant Secretary of the College, Gower Street, W.C.1.

Institute of Psychiatry, London University.—Lecture and demonstration courses for postgraduate students in psychiatry at the Maudsley Hospital. Second term, beginning January 4, 1960. Details from the Dean of the Institute at the Maudsley Hospital, Denmark Hill, London, S.E.5.

Faculty of History of Medicine and Pharmacy.—Inaugural lecture in hall of Worshipful Society of Apothecaries of London, 8.30 p.m., December 2, Canon C. E. RAVEN: "Medicine, Mother of the Sciences."

Central Council for Health Education.—Conference on "Health Education as a Part of Social Work," Friends House, Euston Road, London, N.W.1, January 28, 1960. Details from the Council's Medical Director, Tavistock House North, Tavistock Square, London, W.C.1.

Henry Ford Hospital.—International symposium: "The Blood Platelets," March 17–19, 1960. Details from Dr. S. A. Johnson, Ph.D., Henry Ford Hospital, Detroit, 2, Michigan, U.S.A.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Journal of Ophthalmology.—Issued monthly (£6 annually). The new issue (Vol. 43, No. 9) includes:

SCALPEL AND SCISSORS. J. H. Dobree.
V-Z PROCEDURE FOR THE CORRECTION OF SENILE ECTROPION. A. Urrets-Zavalia, Jr.
EFFECTS OF PARENTERAL IODOACETATE AND OTHER THIOL REAGENTS ON THE RABBIT RETINA: RELATION OF HISTOLOGICAL TO BIOCHEMICAL LESIONS. J. P. Newhouse and D. R. Lucas.
EXPERIMENTS IN HUMAN VOLUNTEERS WITH ADENOVIRUS TYPE 8. Y. Mitsui, L. Hanna, R. Minoda, S. Ogata, H. Kurihara, R. Okamura, and M. Muira.
FUNDUS APPEARANCES IN A CASE OF ACUTE DERMATOMYOSITIS. Stewart Munro.
STUDIES ON DEVELOPING RETINAL VESSELS. VI.—HISTOLOGICAL MEASUREMENT OF FLUORIDE-INDUCED SWELLING IN THE RETINA. C. Pedler.
TRANSIENT TRAUMATIC MYOPIA WITH HYPOTENSION. M. H. Luntz.
BURIED MATTRESS SUTURE FOR CATARACT INCISIONS. C. I. Phillips.
BOOK REVIEWS.
NOTES.

Archives of Disease in Childhood.—Issued six times a year (£4 4s. annually). The new issue (Vol. 34, No. 176) includes:

SOME RESPIRATORY AND CARDIOVASCULAR PROBLEMS AFTER BIRTH. G. S. Dawes.
THE PUPILLARY MEMBRANE IN PREMATURE INFANTS. Bruno Gans.
GLYCOGEN DISEASE. S. van Creveld.
THE SYNDROME OF HYPOPARATHYROIDISM AND STEATORRHOEA. Eirian Williams and Colin Wood.
THE TREATMENT OF CONGENITAL GALACTOSAEMIA. Norman L. Jones and David Leak.
PREGNANCY COMPLICATED BY DIABETES MELLITUS: A STUDY IN COMBINED OBSTETRIC AND PAEDIATRIC MANAGEMENT. Andrew M. Claye and W. S. Craig.
VARICELLA ENCEPHALITIS. J. D. Heppleston, K. M. Pearce, and P. O. Yates.
NEUROLOGICAL SEQUELAE OF PERTUSSIS WITH PARTICULAR REFERENCE TO MENTAL DEFECT. J. M. Berg.
CEREBRAL ATROPHY IN MICROCEPHALIC COUSINS. Peter E. Sylvester.
THE SIZE OF MENTAL DEFECTIVE BOYS. Gordon Dutton.
TREATMENT OF TUBERCULOUS MENINGITIS. W. Morton Fyfe.
PNEUMOCYSTIS PNEUMONIA ASSOCIATED WITH AGAMMAGLOBULINAEMIA. J. G. B. Russell.
PERFORATION OF THE BOWEL IN HENOCH-SCHÖNLEIN PURPURA. R. Basu.
THE NATURAL HISTORY OF THE PARTIAL THORACIC STOMACH (HIATUS HERNIA) IN CHILDREN. I. J. Carré.
BRITISH PAEDIATRIC ASSOCIATION: PROCEEDINGS OF THE THIRTIETH ANNUAL GENERAL MEETING.
BOOK REVIEWS.

British Journal of Preventive and Social Medicine.—Issued quarterly (£3 annually). The new issue (Vol. 13, No. 3) includes:

CROSS-SECTIONAL REVIEW OF MORBIDITY AMONG YOUNG SOLDIERS. S. Rosenbaum.
INVESTIGATION INTO THE WORKING OF THE "DEATH BENEFIT" FOR COAL WORKERS' PNEUMOCONIOSIS. A. L. Cochrane, R. G. Carpenter, and F. Moore.
PEPTIC ULCER IN TOWN AND COUNTRY. C. N. Pulvertaft.
INFLUENCE OF SOME METEOROLOGICAL FACTORS IN THE INCIDENCE OF POLIOMYELITIS. C. C. Spicer.
DURATION OF STAY IN HOSPITAL OF PATIENTS SUFFERING FROM SCHIZOPHRENIA. J. K. Wing, J. Denham, and A. B. Munro.
TRAINING OF STUDENT NURSES. A. Barr.
SOCIAL CLASS DISTRIBUTION OF RESPIRATORY TUBERCULOSIS MORTALITY IN N. IRELAND, 1949-53. J. D. Merrett.
NOTICES.

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, November 30

GUY'S HOSPITAL.—At Physiology Theatre, 5.15 p.m., endocrine demonstration: Tests of Thyroid Function.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor Sheila Sherlock: Hepatic Coma.

ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 4 p.m., Mr. J. Grieve: Physiology of the Urethra.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Professor E. P. Kennedy (Chicago): Biosynthesis of Complex Lipids.

Tuesday, December 1

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. J. L. Gowans: The Lymphocyte.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. H. Marten: The Sweat Retention Syndrome.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-60.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Dr. Henry Miller: Accident Neurosis.

●LIVERPOOL UNIVERSITY: DEPARTMENT OF EXTRA-MURAL STUDIES.—At Medical School, Ashton Street, 7.30 p.m., Professor A. Wilson: Influence of Drugs on Some Endocrine Glands.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. E. H. Belcher: Measurement of Red Cell Life Span.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Dr. R. B. McConnell: Role of Heredity in Gastro-intestinal Disorders.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Dr. H. G. Morgan: Methods of Investigation of Diseases in Bone.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Mr. G. L. Bourne: Anatomy and Physiology of the Amnion and Chorion.

Wednesday, December 2

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Histopathology of Fungous Diseases.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. N. R. Barrett: The Surgery of Pulmonary Tuberculosis.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. D. M. Wallace: Cancer of the Bladder.

LISTERIAN SOCIETY.—At Lecture Theatre, King's College Hospital Medical School, 8.30 p.m., Professor Meyer Fortes, Ph.D.: Family as a Human Institution.

MANCHESTER MEDICAL SOCIETY: SECTION OF MEDICINE.—At Large Anatomy Theatre, Medical School, Manchester University, 4 for 4.30 p.m., Dr. J. Hoenig: Shibboleths in Psychosomatic Medicine.

MIDLAND MEDICAL SOCIETY.—8.15 p.m., Dr. C. H. Stuart-Harris: Recognition, Diagnosis, and Treatment of Virus Diseases.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor G. M. Wilson: Acute Nutritional Changes in Disease.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Mrs. J. E. Hagard: Catering Problems in a Large Industrial Undertaking.

ST. ANDREWS UNIVERSITY.—At Demonstration Room, Department of Medicine, 2.30 p.m., Professor J. L. Henderson, or one of his staff: Some Aspects of Physiology in the Newborn.

Thursday, December 3

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dame Janet Vaughan: Relation of Radiation Dose to Radiation Damage.

LIVERPOOL MEDICAL INSTITUTION.—At Liverpool Royal Infirmary, 2.30 p.m., afternoon clinical meeting.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital School of Medicine, 8 for 8.30 p.m., Right Hon. Lord Justice Morris, P.C.: Giving of Medical Evidence in the Law Courts.

MEDICAL SOCIETY OF THE ROEHAMPTON PLASTIC CENTRE, Queen Mary's (Roehampton) Hospital, S.W.—8 p.m., Mr. Douglas Jackson: Modern Trends in the Treatment of Burns.

NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, 8.30 p.m., Professor J. Trueta: Reflections After Ten Years in the Oxford Chair of Orthopaedic Surgery.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. T. Alper, Dr. M. Ebert, and Dr. R. H. Thomlinson: Biological Effects of Radiation.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Erasmus Wilson Demonstration by Dr. H. G. H. Richards: Problems in Bone Marrow Diagnosis.

ROYAL COLLEGE OF SURGEONS OF ENGLAND AND INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Otolaryngology Lecture by Mr. N. R. Barrett: Hiatus Hernia.

ROYAL PHOTOGRAPHIC SOCIETY: MEDICAL GROUP.—At 16, Princes Gate, London, S.W., 6.30 for 7 p.m., Sir Stanford Cade: What I Want from a Medical Photograph.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Mr. H. J. Seddon: Paralytic Poliomyelitis.

Friday, December 4

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. I. Muende: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. Smart: clinical demonstration.

PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields, 8.30 p.m., Dr. Denis Hill: Psycho-physiology of Murder.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. R. Belsey: Reconstruction of the Oesophagus. (2) 4 p.m., Professor K. W. Donald: Haemodynamics in Common Heart Diseases.

WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—At Board Room, 8.30 p.m., Dr. Donald Teare: Pathology and Homicide.

Saturday, December 5

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Addenbrooke's Hospital, Symposium on Dermatology—Climate and the Skin. *Morning:* At Lecture Room B, 10.30 a.m., Dr G. A. Beck: Light and the Skin; 11.30 a.m., Dr. A. J. Rook: Cold and the Skin; 12.15 p.m., Dr. C. H. Whittle: Heat and the Skin. *Afternoon:* At Outpatient Department, 2.15 p.m., clinical cases. At Lecture Room B, 3.30 p.m., discussion of cases and Any Questions?

KENT PAEDIATRIC AND CHILD HEALTH SOCIETY.—At Children's Department, Farnborough Hospital, 3 p.m., Mr. Frank Dawtry: The Probation Service.

MIDLAND THORACIC SOCIETY.—At Birmingham Medical Institute, 3 p.m., Presidential Address by Mr. S. J. MacHale: Thoughts on Surgical Treatment.

SOUTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At King's College Hospital, S.E., 10.30 for 11 a.m., papers by Dr. J. L. Livingstone, Dr. Samuel Oram, and Dr. M. P. Godfrey.

Sunday, December 6

MANCHESTER UNIVERSITY: FACULTY OF MEDICINE AND COLLEGE OF GENERAL PRACTITIONERS: NORTH-WEST ENGLAND FACULTY.—At Theatre 1, Clinical Sciences Building, York Place, 11 a.m., Professor W. I. C. Morris: Obstetrics.

APPOINTMENTS

BIRMINGHAM REGIONAL HOSPITAL BOARD.—R. J. Bennett, M.B., Ch.B., F.R.C.S., part-time Consultant Ear, Nose, and Throat Surgeon to Stoke-on-Trent group; S. S. F. Munro, M.B., Ch.B., D.O.M.S., part-time Consultant Ophthalmologist to Hereford group; S. J. Crews, M.B., B.Chir., F.R.C.S.Ed., part-time Consultant Ophthalmologist to Birmingham and Midland Eye Hospital; K. Rubinstein, M.D., F.R.C.S.Ed., D.O.M.S., part-time Consultant Ophthalmologist to Birmingham (Dudley Road), (Mental C), (Mental E), and (Sanatoria) groups; Elizabeth Topley, M.D., Deputy Director of Regional Blood Transfusion Service; L. Langton, M.D., F.F.R., M.R.C.P., D.M.R.D., whole-time Consultant Radiologist to Birmingham (Dudley Road) group; F. T. Graves, M.S., F.R.C.S., part-time Consultant Surgeon to Stafford group; P. K. Datta, M.B., B.S., whole-time Senior Casualty Officer to Dudley and Stourbridge group.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—Katharine M. Dormandy, M.B., B.S., M.R.C.P., Senior Registrar in Haematology and Microbiology; W. C. Marshall, M.B., B.S., D.C.H., Assistant Medical Registrar; R. L. Hargrove, M.B., B.S., F.F.A. R.C.S., D.A., Junior Anaesthetic Registrar; I. C. S. Normand, B.M., B.Ch., M.R.C.P., House-physician; A. W. Jansz, M.B., B.S., F.R.C.S., House-surgeon; S. P. Lock, M.B. B.Chir., Registrar in Clinical Pathology; Elizabeth A. Ryan, M.B. B.S., M.R.C.P., and V. Wilson, M.B., B.S., part-time Medical Officers in Dermatology; J. A. Black, M.D., M.R.C.P., Senior Lecturer in Child Health; James Lister, M.B., Ch.B., F.R.C.S.Ed., Senior Lecturer in Paediatric Surgery; E. J. Moynahan, F.R.C.P., Consultant in Dermatology; E. P. O'Sullivan, M.B., B.S., D.C.H., House-physician.

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—P. F. C. Jackson, M.B., B.Chir., F.R.C.S.Ed., M.R.C.O.G., Consultant Obstetrician and Gynaecologist, St. Albans City Hospital, West Herts and St. Paul's Hospitals; W. O. Heffernan, L.R.C.P.&S.I., D.P.M., Assistant Psychiatrist (S.H.M.O.), West Middlesex Hospital; I. F. Hindle, M.B., B.S., Senior Casualty Officer, Luton and Hitchin Group of Hospitals.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Dhanji.—On November 8, 1959, at 1, Kathleen Drive, Kettering, Northants, to Iris (formerly Lewis), wife of Noor Ali Dhanji, M.B., B.S., a sister for Judith Soraya—Helen Zarina.

Gibson.—To Pat (formerly Hughes), M.B., B.S., D.A., and Alfred Gibson, B.D.S., by adoption, a sister for Richard—Deborah Siân (born January 5, 1959).

Lewes.—On November 14, 1959, at Bedford General Hospital, North Wing, to Daphne (formerly Wailes), and David S. Lewes, D.M., M.R.C.P., a brother for Joanna, Virginia, Jane, and Bryony—John Steel.

MARRIAGES

Kay-Butler—Brown.—On October 16, 1959, Julian J. Kay-Butler, M.B., Ch.B., to Hilary J. Brown, of "Greystones," Broughty Ferry, Angus.

DEATHS

Braddon.—On October 29, 1959, at his home, 657, London Road, Thornton Heath, Surrey, William Vaudrey Braddon, B.M., B.Ch.

Chippindale.—On October 30, 1959, in hospital, London, Frederick William Chippindale, M.B., B.S., F.F.A. R.C.S., Surgeon Commander, R.N., aged 55.

Clegg.—On October 19, 1959, in a nursing-home, Bangor, North Wales, Richard Clegg, M.R.C.S., L.R.C.P., formerly of Nelson and Clayton-le-Moors, Lancs, aged 91.

Fetherstonhaugh.—On October 28, 1959, at sea, William Ernest Fetherstonhaugh, M.B., B.Ch., formerly of Calcutta, India, and London.

Ford.—On October 22, 1959, at his home, 21, Baldock Road, Didsbury, Manchester, Herbert Roycroft Ford, M.B., B.Ch., late of 2, Higher Ardwick, Manchester.

Gregory.—On October 20, 1959, at the War Memorial Hospital, Waltham Abbey, Essex, Donald Gregory, M.B., Ch.B., of 160, Honey Lane, Waltham Abbey, aged 41.

Kohler.—On October 20, 1959, at Allermuir, Prudhoe Street, Alnwick, Northumberland, Frederick Ernest Kohler, M.B., Ch.B., aged 62.

MacKenna.—On October 31, 1959, at 6, Hope Street, St. Andrews, Fife, John MacKenna, M.B., Ch.B.

Moffat.—On October 23, 1959, at 224, Thorpe Hall Avenue, Thorpe Bay, Essex, William Johnstone Moffat, M.B., Ch.B., D.P.H., aged 49.

Outhwaite.—On October 22, 1959, in hospital, James Edgar Outhwaite, M.B., Ch.B., of Wood View, Billam's Hill, Otley-in-Wharfedale, Yorks, formerly of Cliffe House, Yeadon, Yorks, aged 60.

Perez.—On October 29, 1959, at Forbes Fraser Hospital, Bath, Som, Victor Perez O.B.E., M.D., Brigadier, late R.A.M.C., retired, aged 65.

Prendergast.—On October 19, 1959, in hospital, John Arnoux Prendergast, O.B.E., of Cleveland Villas, Shipley.

Quine.—On October 30, 1959, at Ballasalla, Isle of Man, Richard Henry Quine, L.R.C.P.&S.Ed., D.P.H., formerly of Pendleton, Lancs, and Frizington, Cumberland, aged 100.

Smith.—On October 30, 1959, at his home, St. Anthony's, Little Gaddesden, Berkhamsted, Herts, George Francis Rawdon Smith, T.D., M.D., F.F.A. R.C.S., aged 77.

Stephenson.—On October 30, 1959, William Stephenson, M.R.C.S., L.R.C.P., of The Croft, Morpeth, Northumberland, late of Newbiggin-by-the-Sea, Northumberland, aged 77.

Wilshaw.—On October 28, 1959, at his home, Lynberry, Wallace Avenue, Worthing, Sussex, Robert Heywood Wilshaw, M.D., M.R.C.P., D.P.H., aged 86.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Spasm in Spastic Paralysis

Q.—*What is the cause of spasm in cases of spastic paralysis? What is the treatment for it?*

A.—The increased muscle tone in spastic paraparesis is due to inhibitory impulses from the brain stem and higher centres being interrupted, with resulting increased activity of spinal reflexes. The flexor spasms which may occur are part of a mass reflex, and they may be precipitated by anything touching the legs. Drug treatment of spasticity is usually disappointing. Curare may diminish or abolish tone by its action on the myoneural junction, but it is of little practical use, since voluntary movement is also abolished, and if a slowly absorbed preparation is given by injection the rate of absorption may be irregular and the respiratory muscles may be affected. Mephenesin is occasionally helpful when given orally in a starting dose of 0.5 g. six-hourly, but often when the dose is large enough to reduce spasticity side-effects such as nausea, giddiness, and diplopia occur and the dose has to be reduced. Meprobamate is also worth trying in a starting dosage of 200 mg. three times daily by the mouth, but here again the results are often disappointing.

Treatment of Post-encephalitic Parkinsonism

Q.—*Have there been any recent advances in the treatment of post-encephalitic Parkinsonism?*

A.—Until recently the standard treatment for Parkinsonism of any kind was the use of drugs of various kinds and often in combination, together with active physiotherapy. Some have thought that the physiotherapy was perhaps more valuable than the drugs, and in no case have the drugs ever succeeded in totally reversing disability, though most feel that they have been helpful. A new form of therapy is now well established—namely, the use of chemical pallidectomy or, more recently, thalamectomy. In the hands of an experienced neurosurgeon the results of the latter operation have to be seen to be believed. Sometimes tremor and rigidity are totally abolished, though power and co-ordination are left intact. Bilateral operations can be carried out, and at the time of writing there is no doubt that in selected cases this procedure is the treatment of choice.

Burning Heels in the Elderly

Q.—*What is the cause and treatment of an intense burning sensation in the heels and elbows of an elderly woman with generalized osteoarthritis?*

A.—The cause of the trouble is pressure. Being stiff in the joints and having flexion contractures, such a patient, who is usually almost immobile and in bed, tends to take undue pressure on her heels and elbows.

She should sit up in a chair dressed in a pair of stockings and leather laced-up walking-shoes with her feet as nearly at right angles to her legs as possible. The chair should be an armchair high enough for her to sit with her thighs at right angles to her legs and her legs at right angles to her feet. The seat of the chair should be such that she can sit upright with her trunk at right angles to her thighs. This position will enable her to take weight on the forearms resting on the chair arms, and not always on her elbows. Alternatively, if convenient and possible, she could support her arms in slings, using sorbo pads to prevent pressure. Application of spirit to the elbows and heels will harden the skin but alone will not relieve the burning sensation.

In some cases the provision of a self-propelled model 3 Ministry of Health wheel-chair, with two large wheels placed anteriorly and two small ball-bearing wheels placed posteriorly, will encourage some activity and ensure the avoidance of elbow pressure. If the flexion contractures are so severe that the use of any chair is impossible, then the legs, too, should be supported in slings so that pressure on the heels is avoided. Even if the patient is confined to bed, her feet should still be supported in shoes as described.

Dermatitis in Cement-workers

Q.—*Is there any way of preventing dermatitis in cement workers? Rubber gloves and silicone creams have been ineffectual.*

A.—The prevention of dermatitis in cement-workers is largely a matter of dust-control and the prevention of skin contact with cement dust. Cement dust causes dermatitis because of its alkalinity and because it is hygroscopic. Consequently, cement rashes are more common in warm weather and in those who perspire freely. If sweating skin can be avoided by adjusting room temperature it will be found to produce some reduction in the incidence of skin disease.

Various opinions have been expressed about the usefulness of barrier cream, but it is generally agreed that the use of rubber gloves is preferable and that these may be donned after first rubbing lanoline or a similar cream into the skin. It might be worth while trying gloves made of some of the newer plastics which permit water vapour to pass through them but will prevent contact of the skin with cement dust. The arrangements for washing are of great importance in that only bland soaps should be used, adequate drying facilities should be available, and a fatty cream should be provided for use after washing.

Prophylactic Antibiotics in Clean Surgery

Q.—*Is there any sound evidence to show that the incidence of post-operative wound sepsis is lessened if antibiotics (especially penicillin) are used prophylactically in "clean" surgery, assuming efficient aseptic surgical technique? I refer to both systemic and topical antibiotics.*

A.—With "efficient aseptic surgical technique" there should certainly be no need for the use of antibiotics either systemically or locally. It has been suggested that the adoption of routine antibiotic cover for clean cases is likely to lead to some slackness in the rigid discipline of surgical asepsis—a result to be deplored, as is also the production of resistant organisms.

There is, of course, the type of case in which, although the operation is a "clean" one, there is a possibility of latent infection being present. A simple example would be that of the excision of a bursa that had previously been infected. In such cases the local use of appropriate antibiotics would be justified. If post-operative sepsis occurs after a truly clean operation the cause must be searched for and, when found, eliminated. This is a better method of dealing with the situation than aborting the infection by the use of antibiotics.

Muscle Fasciculation

Q.—*What is the physiology and pathology of muscle fasciculation? Is it possible to differentiate benign forms, if any, from those of more unfavourable prognosis?*

A.—Muscle fasciculation occurs in disease of the spinal anterior horn cells, most typically in motor-neurone disease but also in syringomyelia and spinal-cord tumours and sometimes in the acute stage of anterior poliomyelitis. There is also a benign type of muscle fasciculation not associated with disease of the central or peripheral nervous system in which fasciculation may occur intermittently for many years, and, particularly when the condition affects doctors or medical students, it may be accompanied by considerable anxiety. This type can be distinguished clinically by the complete absence of muscle wasting or weakness and by

the absence of changes in the reflexes, even though the fasciculation may have persisted for many months.

The physiology of muscle fasciculation is not thoroughly understood. In normal people it occurs after an injection of neostigmine, a drug which is thought to act principally at the myoneural junction, and in patients with motor neurone disease it may continue after a motor nerve has been blocked by a local anaesthetic or divided—findings which suggest a peripheral mechanism for the phenomenon.

Paint-spraying and Lung Cancer

Q.—*Is inhalation of paint during spraying a factor in the aetiology of carcinoma of the lung?*

A.—The Registrar-General's *Decennial Supplement on Occupational Mortality* for 1951[1] indicates that deaths from cancer of the lung among paint-sprayers and aerographers is high but not significantly so, the standard mortality ratio being 102. The following table of the number of deaths registered in 1951 and the number expected in three age-groups of these workers appears in the *Decennial Supplement*. The excessive deaths from lung cancer occur mainly in the age-group 55–64:

	Age 20–45		Age 45–55		Age 55–64	
	Reg.	Exp.	Reg.	Exp.	Reg.	Exp.
Cancer of lung and bronchus ..	7	5	11	11	18	11

There appears to be a higher incidence of cancer of the stomach in the younger age groups.

REFERENCE

1 Registrar-General, *Decennial Supplement on Occupational Mortality*, 1951, vol. I, part 2. H.M.S.O., London.

Serum Mucoid Test

Q.—*What is the serum mucoid test, and what is its value?*

A.—Seromucoid is one name for the serum glycoproteins or mucoproteins which are not precipitated by perchloric acid. They contain relatively high proportions of carbohydrate strongly bound to the protein component. The concentration of seromucoid is increased in pregnancy, cancer, rheumatoid arthritis, tuberculosis, and most infective and febrile diseases, and seems to correlate well with the clinical activity, at least in rheumatic fever; it is raised after injection of bacterial pyrogens, A.C.T.H., or parathyroid extract, and after surgical operations. It seems to be involved quite non-specifically as part of a reaction to many unrelated pathological stimuli.

The simplest method for estimation seems to be that of de la Huerga *et al.*[1]; those of Keyser,[2] Hess *et al.*,[3] and Jirgl[4] may not measure the same thing and are more complicated.

Comments on the significance of the results and further references will be found in Kushner *et al.*[5] and Stidworthy *et al.*[6]

REFERENCES

1 Huerga, J. de la, Dubin, A., Kushner, D. S., Dyniewicz, H. A., and Popper, H., *J. Lab. clin. Med.*, 1956, 47, 403.
2 Keyser, J. W., *J. clin. Path.*, 1950, 3, 106.
3 Hess, E. L., Coburn, A. F., Bates, R. C., and Murphy, P., *J. clin. Invest.*, 1957, 36, 449.
4 Jirgl, V., *Klin. Wschr.*, 1957, 35, 938.
5 Kushner, D. S., Honig, K., Dubin, A., Dyniewicz, H. A., Bronsky, D., Huerga, H. de la, and Popper, H., *J. Lab. clin. Med.*, 1956, 47, 409.
6 Stidworthy, G., Payne, R. W., Shetlar, C. L., and Shetlar, M. R., *J. clin. Invest.*, 1957, 36, 309.

Closure of Anterior Fontanelle

Q.—*What are the likely causes of delayed closure of the anterior fontanelle, which is markedly depressed, in an African child, aged 2, who is apparently physically and mentally normal and does not look hydrocephalic?*

A.—The age of 2 is certainly rather late for the fontanelle to remain open, but there is a wide range in the age of closure, and it is still possible that this is simply a normal late closure. Pathological causes for failure of normal bone growth come next in the possibilities, with rickets the most probable cause. Osteogenesis imperfecta is very unlikely; craniocleidodysostosis is another rare disease which could be responsible. Cretinism must be considered. Raised intracranial tension as a cause is ruled out by the fact that the fontanelle is depressed and the normal size of the skull excludes hydrocephalus. Of all these possible causes, rickets is most likely.

NOTES AND COMMENTS

Battery-operated Photoelectric Haemoglobinometer.—Dr. R. M. WINSTON (Salford) writes: I do not agree with the advice given by your expert about a battery-operated haemoglobinometer for use in a mission hospital in Africa ("Any Questions?" October 10, p. 707). Africa is very big, with much variation in climate, but most, if not all, mission hospitals in Africa are in places which have one or more hot and humid months each year. My personal experience in Lagos, Nigeria, appears therefore to be apposite. I and others used the M.R.C. photometer in Lagos, but we found it most unsuitable for reasons which I published in 1954.[1] The worst problem with which the mission doctor will have to contend, if he uses the M.R.C. photometer, will be the appearance of spots due to moulds and fungi growing in the grey-wedge. Also the only satisfactory method of detecting these spots is to dismantle the grey-wedge and inspect it. A single standard, because it checks only a small area of the grey-wedge, is an almost valueless check. In Lagos I found the E.E.L. colorimeter satisfactory. Filters required replacing fairly often and both spare selenium cells and bulbs had to be available, but a good cell and bulb would last for months. This colorimeter uses a low voltage bulb and could easily be wired to run from batteries. A model used to be available for running from batteries or mains and may still be on sale. The problem of calibration for haemoglobin estimation was solved by using the alkaline haematin method, running Gibson and Harrison's artificial standard weekly and whenever the selenium cell or bulb was changed.

REFERENCE

1 Winston, R. M., *W. Afr. med. J.*, 1954, 3, 3.

OUR EXPERT replies: Dr. Winston has had much more experience in Africa than I have, and I would add to his remarks that nearly all the photoelectric instruments available in this country can be run off batteries, including the Gallenkamp, which is based on King's original pattern. I think that even Dr. Winston's solution is not completely satisfactory, because he agrees that you have to change filters frequently, and my experience is that selenium cells have a very variable life. The problem is exactly that which all scientific workers in hot and humid climates suffer from, and one's attitude is bound to be conditioned by the particular solution which your colleagues have recommended. For a small instrument, such as an M.R.C. photometer, it should not be impossible to keep it in a dehydrating box except when in actual use. I believe that this has been done in several large laboratories where air-conditioning was not practicable.

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